Evidence based management of hepatitis

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Colofon

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1 General introduction

Introduction

Hepatitis is defined as the structural changes in the liver that arise as a result from an inflammatory stimulus. Histological, it is characterized by the presence of inflammatory cells in the tissue of the liver. Hepatitis runs a dichotomous course. Either it is self-limiting with complete reversal of pathological changes or it can progress to fibrosis (scarring) and cirrhosis.

Hepatitis may occur with limited or no symptoms, but in advanced stages it often leads to jaundice, anorexia (poor appetite), and malaise. Persistence of hepatitis for more than six months is classified as chronic hepatitis. Hepatitis caused by a hepatitis virus (for example hepatitis B, C, and D virus) are responsible for the overall majority of hepatitis cases worldwide. Hepatitis may also be caused by toxic substances (for example alcohol and medications), other infections, and autoimmune diseases.[1]

This thesis focuses mainly on autoimmune hepatitis, hepatitis delta, and hepatitis C infection and the therapeutic options for these hepatological disorders. The last 20 years have witnessed an impressive development of clinical care options for patients with various forms of hepatitis. This progress has come through development of drugs but also by improvement of non-medical devices such as stents. Especially in the area of chronic hepatitis C the number of new antiviral drugs is increasing rapidly. These new drugs lead to the question how to best use them for which patient and for which (phase of the) medical condition. This progress leads to many questions and as such clinicians more and more rely on results stemming from evidence based medicine. Evidence based medicine is the explicit and judicious use of current best evidence and clinical expertise in making decisions about the care of patients. As such, it requires the integration of individual clinical expertise with best evidence that is present in the literature. The "best evidence" usually stems from randomized clinical trials that compare the efficacy of a therapy with standard-of-care or placebo in a well-defined patient population.

There is little doubt that evidence based medicine has its merits. Well executed clinical trials provide new evidence that helps decision making in clinical practice. When we are introducing new therapies that replace old well known management options we must be certain that these options are more powerful, more efficacious, more accurate, and last but not least also safe.

There is an uneven penetration of evidence based medicine within hepatological disorders. For some forms of hepatitis, for example hepatitis C infection, there is a wealth of clinical information from well executed randomized trials available that are helpful to assist the clinician. For other disorders such as hepatitis D, or autoimmune hepatitis there is a paucity

of evidence. In addition, trials have been executed differently and they differ in methodological quality which contributes to the lack of powerful data that help us in clinical decision making. Most of the executed trials included only few patients. Moreover, trials performed decades ago have not used current standardized, universally accepted end-points or diagnostic criteria. Without any doubt, most trials included some forms of bias, which lead to uncertainties and different treatment results.

In order to progress it is of eminent importance to start to collect the information that is available that best summarizes the current clinical thinking. In this respect, evidence based medicine can be used as method for clinical problem solving. It may provide us with ways of determining rational practice, methods to integrate service to our patients with training and education, and it may act as a model to generate ideas to improve care through research.

This thesis focuses mainly on a selection of questions in the three types of hepatitis mentioned, autoimmune hepatitis, hepatitis delta, and hepatitis C virus infection. In general, we addressed these questions by performing systematic reviews. In addition, we collected information on the quality of the performed randomized clinical trials which were included in our systematic reviews with an aim to make recommendations on how to optimize new clinical trials in the hepatitis field in the future.

Autoimmune hepatitis

Epidemiology/Pathogenesis

Autoimmune hepatitis is a rare chronic progressive liver disease of unknown etiology.[2] Clinical presentation may include fatigue, pain in the right upper quadrant of the abdomen, polymyalgia, and arthralgia involving small joints.[2] The disease predominantly affects women and occurs in children and adults of all ages. The estimated annual incidence of autoimmune hepatitis among Northern Europeans is 1.9 cases per 100,000 persons per year.[2, 3] The clinical picture is heterogeneous and in absence of a single clinical or biochemical test, diagnosis is made according to a set of clinical criteria developed in 1993, which were revised in 1999 and simplified in 2008.[4-6] These diagnostic criteria include (1) hypergammaglobulinemia; (2) the presence of particular autoantibodies, i.e., antinuclear antibodies (ANA), smooth muscle antibodies (SMA) or liver kidney microsomal antibodies (anti-LKM1); (3) liver histology features similar to chronic hepatitis of other etiology; (4) the absence of viral and toxic hepatitis or other conditions that may resemble autoimmune hepatitis.[6, 7] According to the presence of autoantibodies, a sub classification into two

major types – Type 1 autoimmune hepatitis and type 2 autoimmune hepatitis – has been proposed. Type 1 autoimmune hepatitis is the most common form of the disease, it is characterized by the presence of ANA and/or SMA. Type 2 autoimmune hepatitis is associated with the presence of anti-LKM1.[8]

The pathogenesis of autoimmune hepatitis is uncertain, but it probably involves a cell-mediated form of cytotoxicity. An unknown virus, drug or environmental toxin may be the triggering factor or the disease may occur spontaneously.[9]

Treatment

Ten-year survival has ranged from 85% to 95%.[10-13] Recent long-term studies reporting a 2-fold higher mortality than that of the general population.[14, 15] Treatment with predniso(lo)ne, usually in combination with azathioprine, dramatically improved survival and is considered the mainstay of therapy for autoimmune hepatitis.[16] This therapy originates from the 1970s, when three randomized clinical trials have established the effect of immunosuppressive therapy for autoimmune hepatitis.[16-18] Predniso(lo)ne monotherapy or a combination of predniso(lo)ne and azathioprine was superior to other treatment options, including titrating prednisone, in improving liver function and life expectancy. [16-18] However, in some cases cirrhosis develops despite treatment. In other patients, treatment discontinuation or dose reduction is necessary because of intolerable adverse events.

This thesis addresses the **question**: what is the optimal induction and subsequent maintenance therapy for autoimmune hepatitis? We therefore performed a systematic review and examined all randomized clinical trials for treatment of autoimmune hepatitis published from 1950 until July 2009 (**model**). We hypothesized that therapy of predniso(lo)ne with or without azathioprine is more effective than other (immunosuppressive) drugs in achieving remission and limiting mortality.

Hepatitis delta

Epidemiology/Pathogenesis

Hepatitis delta virus was first identified in 1977 in serum of hepatitis B surface antigen (HBsAg) carriers, during a major outbreak of hepatitis delta in the Mediterranean basin.[19, 20] Hepatitis delta is a parenterally transmitted ribonucleic acid (RNA – HDV RNA) virus that requires hepatitis B virus surface proteins to form the viral coat and to infect hepatocytes. Worldwide, 15-20 million people are estimated to be anti-hepatitis delta virus positive.[21,

22] However, it is possible that these estimates are inaccurate and difficult to determine as systematic screening is not performed in hepatitis b-infected individuals, especially if they present with normal liver enzymes.[23] The prevalence of hepatitis delta infection in industrialized countries has declined as a result of anti-hepatitis B virus vaccination; however, epidemiologic data show that hepatitis delta-related diseases persist in several regions of the world.[20] Hepatitis delta infection can be distributed in eight genotypes. Each genotype has a unique geographical representation.[24-32]

Hepatitis delta is spread and bears the same transmission risk as hepatitis B, through parenteral or sexual exposure to blood or body fluids. Infection with hepatitis delta can occur in two major patterns: as co-infection and as superinfection. Both patterns of infection may lead to chronic liver disease and progression to cirrhosis in 80% of infected patients.[33-39]

Treatment

The ultimate goal of treatment is to eradicate hepatitis delta together with hepatitis B. Hepatitis delta is considered eradicated when both HDV RNA in the serum and HDAg in the liver become persistently undetectably. However, it is only with HBsAg clearance that complete and definitive resolution is attained. Viral clearance is accompanied with normalization of the alanine aminotransferase (ALT) level, amelioration of liver inflammation, while the progression of liver fibrosis stops. This is the ultimate treatment goal, however, with current means treatment remains difficult. Interferon-alpha is the only therapy that bears some efficacy against hepatitis delta. Indeed anecdotal evidence suggest that in isolated cases virological, biochemical, and histological response may be obtained.[40-43] Randomized clinical trials conducted so far have failed to show that (combination) therapy with ribavirin, famcyclovir, lamivudine, levamisole, and thymosin have an improved efficacy compared to interferon-alpha monotherapy.[44-49]

At the outset of this thesis, high dose of recombinant standard interferon-alpha was the preferred option for experts dealing with these patients. Although pegylated interferon-alpha (peg interferon-alpha) is significantly superior to standard interferon-alpha for treatment of both chronic hepatitis B and C, its superiority has not been elucidated in the hepatitis delta therapy.[50, 51]

Since there appears to be an important therapeutic role or (peg) interferon-alpha therapy in the treatment of hepatitis delta, an in depth assessment of the evidence that supports efficacy and safety of interferon-alpha based strategies in hepatitis delta is warranted.

To this end, we wanted to address the **question** what the available evidence for interferon-alpha in hepatitis delta therapy currently is? Therefore, we performed a systematic review and examined all randomized clinical trials that investigated interferon-alpha-based treatment in hepatitis delta published from 1970 until January 2011 (**model**). We hypothesized that peg interferon-alpha therapy is more effective than treatment with interferon-alpha in achieving undetectable levels of HDV RNA and normal levels of ALT.

Hepatitis C infection

Epidemiology/Pathogenesis

Hepatitis C virus infection was first described in 1989.[52] Presence of hepatitis C virus RNA (HCV RNA) for more than 6 months delineates a chronic hepatitis C infection. It is thought that chronic hepatitis C affects around 3%, i.e. 170 million individuals worldwide.[53-55] The prevalence in The Netherlands varies between 0.1-0.4%.[56, 57] European prevalence rates, especially in southern European countries are somewhat higher (0.4-4%).[58]

At least 6 different hepatitis C genotypes (1-6) and several subtypes (a, b, etc.) have been identified.[59] Globally, genotype 1 to 4 are the most common causes of chronic hepatitis C.[59] In The Netherlands, ~50% of chronic hepatitis C is caused by genotype 1a and 1b, ~30% by genotype 3, whereas genotype 2 and 4 both account for ~10% of chronic hepatitis C infected patients. Genotype 5 and 6 are uncommon in The Netherlands.[60-62]

Hepatitis C infection is a leading cause of mortality and liver-related morbidity with hepatic fibrosis, end-stage liver cirrhosis, and hepatocellular carcinoma as the dominant clinical sequelae.[54] Hence, prevention of progression is important. Chronic hepatitis C infection progresses slowly, over a time frame of 15 years to 50 years. Around 10-20% of all infected individuals will develop end-stage liver disease (cirrhosis).[63-68] In cirrhotic hepatitis C infected patients, the annual occurrence of hepatocellular carcinoma is 1% to 4%.[69]

Treatment

Prevention of progression to development of cirrhosis is possible with targeted antiviral treatment. Successful antiviral treatment is defined as reaching a sustained virological response (SVR), that is, clearance of HCV RNA from the blood six months after stopping treatment. Unfortunately, current antiviral therapy does not reach SVR in 100% of treated patients.

According to guidelines, antiviral therapy for chronic hepatitis C infection, consist of a combination of peg interferon-alpha and ribavirin for all genotypes.[70, 71] The regimen may include either peg interferon-alpha-2b (Peg-Intron®) or peg interferon-alpha-2a (Pegasys®). Both agents are administered subcutaneously with weekly intervals.[72] The optimal dose of peg interferon-alpha-2b is 1.5 µg/kg/week.[72] Peg interferon-alpha-2a is administered at a fixed dose of 180 µg weekly.[72] Ribavirin is an oral therapy with weight-based total daily doses between 800 mg and 1200 mg administered twice per day.[73] Forty percent to 80% of chronic hepatitis C infected patients without co-infection with hepatitis B virus or human immunodeficiency virus will achieve SVR after treatment with peg interferon-alpha and ribavirin.[72, 74]

Treatment for chronic hepatitis C underwent a paradigm shift with the introduction of a new class of antiviral drugs for hepatitis C virus genotype 1. These antiviral agents act directly, inhibiting the nonstructural (NS) NS3/N4A serine protease and NS5B polymerase of the hepatitis C virus. The direct-acting antivirals (DAAs) can alone or in combination with peg interferon-alpha and ribavirin (triple therapy) increase sustained virological response rates. From April 2012 onwards two DAAs boceprevir (Victrelis®) and telaprevir (Incivo®) have been allowed on the market in The Netherlands and are reimbursed by the health insurance companies for the treatment of chronic hepatitis C genotype 1 infection in adults with compensated liver disease (including cirrhosis). These two DAAs which have to be given in combination with peg interferon-alpha and ribavirin, can increase SVR rates considerably, from 40-50% to 70% or above.[75-79] Currently, phase III clinical trials with drugs such as ledipasvir, daclatasvir, and sofosbuvir have reached the journals.[80-82]

Success in terms of SVR are influenced by several host dependent factors but also viral factors. One of the major elements that influences SVR is viral genotype.[83] Patients infected with genotype 2 and 3 respond better to antiviral treatment than patients infected with genotype 1 and 4.[83]

Apart from (peg) interferon-alpha and ribavirin, a great number of drugs have been investigated in chronic hepatitis C. Aminoadamantanes, another antiviral group, such as amantadine and rimantadine, have also been investigated in several trials for treatment of patients with chronic hepatitis C.[84, 85] Amantadine, which has been used primarily for the prophylaxis and treatment of respiratory tract infections caused by influenza A virus, is believed to interfere with early stages of viral replication, uncoating or primary transcription of viral RNA.[86, 87] Aminoadamantanes, mostly amantadine, were investigated as oral

monotherapy, administered mostly as 100 mg twice a day, and also in combination with interferon-alpha or ribavirin, or both.

With the new DAAs, higher SVR-proportions can be reached, but still not 100%.[75-79]. This indicates that there is an unmet need for drugs with better efficacy. The data from randomized clinical trials that have been performed so far have created more questions than anticipated. For example, are there other drugs available that increase SVR-proportions? Or did we overlook drugs that are available and have been investigated in formal randomized clinical trials but were disregarded because they failed to increase the overall SVR rates. These drugs may be useful and effective for certain subpopulations. Trials investigating aminoadamantanes in chronic hepatitis C demonstrated conflicting results. Some trials showed a beneficial effect of the addition of the aminoadamantane amantadine. Also, different trials demonstrated efficacy in a subgroup with patients who were difficult to treat, with interferon non-response.[88, 89] Other trials showed no enhancement of achieving SVR.[90, 91]

We wanted to answer the **question** whether the administration or addition of aminoadamantanes to chronic hepatitis C treatment is beneficial? This is necessary as the results from the clinical trials highly varied and its use continued in clinical practice. Therefore, we performed a systematic review with meta-analysis aimed at assessing benefits and harms of aminoadamantanes (**model**). We hypothesized that aminoadamantanes improves SVR in some subgroups, for example patients with an interferon dependent non-response.

Furthermore, we wanted to write a new Dutch guideline for hepatitis C virus infection that provides recommendations for the management of hepatitis C infection. The last Dutch guideline on the treatment of hepatitis C infection stems from 2008.[92] As mentioned, until 2012 the standard for treatment consisted of peg interferon-alpha and ribavirin. The advent of first-generation direct antiviral agents such as boceprevir and telaprevir has changed the concept of treatment of adult chronic hepatitis C genotype 1 infected patients. In order to guide the clinician through the changed therapeutic environment we want to provide a completely revised guideline with concise recommendations for the management and treatment of hepatitis C monoinfection in adults. The Dutch guideline serves as a manual for physicians for the management and treatment of acute and chronic hepatitis C monoinfection.

Research models

In order to address the abovementioned questions we applied the systematic review as main research tool. We performed systematic reviews of randomized clinical trials for the various topics that have been published in the international literature. In order to answer a specific research question, a systematic review attempts to compare and collect all available evidence. In order to minimize bias, we used a systematic method that provides more reliable findings. On the basis of these findings it is possible to draw conclusions and provide input for clinical decisions.[93, 94]

Key characteristics of a systematic review are: clear objectives with pre-specified eligibility criteria for trials; an explicit, reproducible methodology; a systematic search that attempts to identify all trials that would meet the eligibility criteria; an assessment of the validity of the findings of the included trials, for example through the assessment of risk of bias; and a systematic presentation, and synthesis, of the characteristics and findings of the included trials.[95]

In order to answer our specific research questions we performed four systematic reviews following the above mentioned steps. We performed two of these four systematic reviews according to the Cochrane systematical review method. This Cochrane method has been developed by The Cochrane Collaboration, which prepares, maintains, and promotes systematic reviews to inform healthcare decisions.[95] The Cochrane method distinguishes itself by using a uniform format for all Cochrane systematical reviews. Standard headings and tables are embedded in the Cochrane Collaboration's Review Manager (RevMan) software. This guides the authors when preparing their report and make it easier for readers to identify information that is of particular interest to them. Furthermore, protocols for Cochrane reviews are published in the Cochrane Database of Systematic Reviews prior to publication of the Cochrane review, which reduces the impact of authors' bias, promotes transparency of methods and processes, reduces the potential for duplication, and allows peer review of the planned methods.[95]

Besides the systematic review as main research tool, the clinical guideline was the other used method. Clinicians need simple, patient specific, user friendly guidelines. There are three components which are essential building blocks of usable clinical guidelines. The first is the explicit identification of the major decisions that are relevant to patients, which have to be made, and the possible consequences of these decisions. Weighing the various consequences of different treatment options, decisions and their consequences are often difficult to map and a flow diagram or algorithm that identifies the key decisions and important outcomes relevant to patients and others is crucial. This is a requirement to limit practice variation.

The second key success parameter involves bringing together the relevant, valid evidence that clinicians need to make informed decisions at each of the key decision points. In every field there are controversies and gaps in knowledge and sifting through the evidence that is inadequate is difficult but a necessity. The final goal is to make explicit statements about the benefits and risks of treatment in view of patient preferences and available resources. A third essential component of a successful guideline is the presentation of evidence and recommendations in a concise, accessible format. Decision makers must be able to retrieve and assimilate information quickly. Moreover, information must be presented in a flexible format that is applicable to specific patients or circumstances.

Outline of the thesis

In **Chapter 1**, 'the General Introduction', we provide background information and we describe a framework for this thesis. **Chapter 2** describes systematically the optimal induction and subsequent maintenance therapy for autoimmune hepatitis. In **Chapter 3** we will systematically review the evidence for interferon-alpha in hepatitis delta virus therapy. We will delineate treatment with aminoadamantanes versus placebo or no intervention for chronic hepatitis C infection in **Chapter 4** according to the Cochrane systematical review method**. Chapter 5** also follows the Cochrane systematic method and focuses on treatment with aminoadamantanes for chronic hepatitis C infection, but in this case compared with other antiviral drugs. In **Chapter 6** we will describe the current treatment guidelines of chronic hepatitis C virus infection. We will complete this thesis by a General Discussion (**Chapter 7**) that summarizes and discusses the main findings of this thesis.

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A Autoimmune hepatitis

2

Treatment options for autoimmune hepatitis: a systematic review of randomized controlled trials

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Abstract

Introduction: Predniso(lo)ne with or without azathioprine is considered the mainstay in the treatment of autoimmune hepatitis (AIH), but many therapeutic options are available. The primary objective of this review was to explore the published literature on the optimal induction and subsequent maintenance therapy for AIH.

Methods: We performed a systematic search on electronic databases MEDLINE (1950-07.2009), Web of Science and Cochrane and the website www.clinicaltrials.gov. Randomized controlled trials (RCTs) on apparent beneficial treatment regimens as induction or maintenance treatment in AIH were included. Pediatric studies were excluded. We calculated relative risks (RR) for comparison of treatment options on the primary outcome measure, which was defined as clinical, biochemical and histological remission.

Results: Eleven RCTs were included, of which 7 studies evaluated the induction therapy in AIH patients: 3 treatment-naive (n = 253), 2 relapse (n = 53), 2 combination of naive and relapse (n = 110). The remaining 4 studies (n = 162) assessed maintenance therapy. All but one maintenance study (thymostimulin versus no therapy) studied predniso(lo)ne (PRED), azathioprine (AZA) or combination PRED+AZA. We found no differences in primary outcome between induction therapy with PRED and PRED+AZA in treatment naive patients (RR=0.98; 95%CI 0.65-1.47). AZA monotherapy as induction was considered as not viable because of a high mortality rate (30%). This was similar in AIH patients who relapsed: RR for PRED vs PRED+AZA for inducing remission was not different: 0.71 (95%CI 0.37-1.39). PRED+AZA maintained remission more often than PRED (RR=1.40; 95%CI 1.13-1.73). Also AZA maintained a higher remission rate than PRED (RR=1.35; 95%CI 1.07-1.70). Maintenance of remission was not different between PRED+AZA and AZA (RR=1.06; 95%CI 0.94-1.20).

Conclusions: Based on available RCTs PRED monotherapy and PRED+AZA combination therapy are both viable induction therapies for AIH treatment naives and relapsers, while for maintenance therapy PRED+AZA and AZA therapy are superior to PRED monotherapy.

Background

Autoimmune hepatitis (AIH) is a rare chronic progressive liver disease of unknown etiology.[1] Clinical presentation may include fatigue, pain in the right upper quadrant of the abdomen, polymyalgia, and arthralgia involving small joints.[1] The disease predominantly affects women and occurs in children and adults of all ages. The estimated annual incidence of AIH among Northern Europeans is 1.9 cases per 100,000 persons per year.[1,2] The clinical picture is heterogeneous and in absence of a single clinical or biochemical test, diagnosis is made according to a set of clinical criteria developed in 1993, which were revised in 1999 and simplified in 2008.[3,4,5] These diagnostic criteria include: 1) hypergammaglobulinemia; 2) the presence of particular autoantibodies, i.e. ANA, SMA or anti-LKM1; 3) liver histology features similar to chronic hepatitis of other etiology; and 4) the absence of viral and toxic hepatitis or other conditions that may resemble AIH.[5,6] Based on this set of criteria, the sensitivity of the scoring system for AIH ranges from 97%-100%, and its specificity for excluding AIH in patients with chronic hepatitis C ranges from 66%-92%.[6]

Three randomized controlled trials (RCTs) dating from the 1970's have established the effect of immunosuppressive drugs for AIH.[7-9] Predniso(lo)ne monotherapy (PRED) or a combination of predniso(lo)ne and azathioprine (PRED+AZA) was superior to other treatment options, including titrating PRED, in improving liver function and life expectancy.[7-9] The current recommendations for AIH therapy originate from this era, and PRED, usually in combination with AZA, is considered the mainstay of therapy. In some cases cirrhosis develops despite treatment; or treatment discontinuation or dose reduction is necessary because of intolerable adverse events. This has fueled the search for treatment alternatives.

Our primary objective was to explore the published literature on evidence of optimal induction and subsequent maintenance therapy for AIH. We therefore performed a systematic review and examined all RCTs for treatment of AIH published from 1950 until present.

Methods

Literature search

We performed a systematic literature search using a set of electronic databases: MEDLINE (1950-07.2009), Web of Science and Cochrane and the website www.clinicaltrials.gov to identify all published articles and abstracts, and ongoing studies from 1950 until July 2009.

The following terms were used: 'hepatitis', 'autoimmune' and 'clinical trial'. All papers published before August 2009 were eligible.

Selection of studies

We employed a 2-stage approach. First, we excluded all articles that were not written in English, German, French or Spanish. We subsequently removed all duplicates, and screened remaining articles on basis of title and abstract. Only RCTs were included: case reports, case series, review articles, letters and editorials were excluded. Studies not evaluating the efficacy of therapy for AIH in adult patients (age ≥18 years) were rejected. Subsequently, full text screening was applied to the remaining studies. Articles were systematically reviewed on the basis of their inclusion criteria and methodological aspects by two independent reviewers (ML, MP). Discrepancies were solved by discussion with a third party (JD). In order to check whether our search included all published papers that were possibly relevant for this review, we scrutinized reference lists of included articles. This strategy was adopted because of evolving definition of AIH prior to 1993.

Outcomes

Remission was considered as the primary outcome measure. We defined remission following recently published criteria: disappearance of symptoms; normal serum bilirubin and γ-globulin levels; serum aminotransferase level normal or less than twice normal; normal hepatic tissue or minimal inflammation and no interface hepatitis.[10] For each individual article, we evaluated all available outcomes that matched the criteria of our user definition of remission. For example, if liver biopsy was not an outcome described in a particular article, we applied all other presented outcomes, such as clinical and biochemical variables, in order to achieve the most appropriate definition of remission for that study.

The secondary outcome measures included mortality and occurrence of adverse events. All outcomes were extracted from the included trials and were assessed at maximum follow-up.

Clinical trials in the treatment of AIH can be divided in 2 categories: 1) trials that assess the effect of induction therapy in newly identified or relapsed AIH patients (induction trials); and 2) trials that have been performed during remission in order to compare the efficacy of two immunosuppressive regimens with maintenance of remission as the primary endpoint (maintenance trials).

Quality of the included studies was assessed, based on a well-established, validated scale developed by Jadad et al.[11] The Jadad score gives a numerical score between 0-5 as a rough measure of clinical trial design/reporting quality (0 being weakest and 5 being strongest).

Extraction of data

After inclusion, we extracted data from each article and entered characteristics of trials, patients, and interventions, as well as the primary and secondary outcome measures. Trial characteristics included the first author's name, year and journal of publication, study design, type, dose and duration of applied therapy and length of follow-up. Patient characteristics comprised inclusion and exclusion criteria, mean age, number of patients randomized, and number and reasons for dropouts and withdrawals.

Data on all patients, irrespective of compliance or follow-up were sought to allow intention-to-treat analyses. In this analysis the total number of patients randomized is the number of patients included in the efficacy analysis. We used data related to initial therapy and relevant to maintenance therapy. In case data were recorded immediately at the end of the evaluation period, this was preferred to follow-up data. In case of missing outcome values at the end of the evaluation period, due to premature withdrawal of therapy in patients with deterioration or drug intolerance, last measured values of outcome were substituted for missing values.

In order to evaluate adverse events related to therapy for AIH, data regarding adverse events in patients treated with the interventional drug(s) were extracted. In addition, data about deterioration in all patients reported in the included studies, were extracted.

Synthesis of data and analysis

In this review, a brief overview of the interventions and number of patients in the trials is given for each separate study. In addition, we pooled patient data of all studies and stratified them in different subgroups according to induction and maintenance therapy, applied intervention and obtaining remission, mortality or complications. This was done in order to determine the efficacy of the interventional drugs in terms of induction of favorable outcome in each of the different therapy groups.

We calculated overall frequencies for the primary outcome measure expressed as percentages. Furthermore, frequencies and percentages for two of the secondary outcome measures, reported mortality and adverse events were calculated.

Data was stored in Reference Manager 11 and Excel database software for Windows XP. Due to heterogeneity of studies, we have focused on descriptive analysis and overall frequencies of favorable outcomes were determined by sample sized weighted pooled proportion. In order to quantify the differences between frequently studied treatment strategies we pooled the data and calculated relative risk with 95% confidence interval.

Results

Literature search and selection of studies

The results of our systematic literature search and subsequent selection of articles are summarized in a flow diagram (Figure 1). The search identified 302 different studies, of which we excluded 247 studies due to study aims; 49 studies were rejected because of study design. Full text screening was applied for 6 articles, and all fulfilled the selection criteria. Of these articles, the reference lists were checked, and this strategy resulted in 5 additional articles that fulfilled the inclusion criteria. Thus, a total of 11 RCTs were included for further analyses[7-9,12-19] of which 7 studies evaluated the induction therapy in AIH patients: 3 treatment-naive (n = 253), 2 relapse (n = 53), 2 combination of naive and relapse (n = 110). The remaining 4 studies (n = 162) assessed maintenance therapy.

Many drugs were studied and we analyzed the most viable options: PRED, AZA or a combination of both. Outcome assessments in patients treated within the different treatment arms were made after an evaluation period of >3 months, the mean evaluation period was for the groups comparable, and varied between 1-2 years.

Induction therapy in treatment naive AIH patients

We retrieved 5 studies, published between 1971 and 1982, that assessed the clinical outcome of AIH in drug naive patients (Table 1). These 5 studies included 363 patients in 6 different arms, 26% were male.[7-9,17,18] The calculated Jadad score of these studies ranged between 1 and 4. Two studies performed a head-to-head comparison between PRED and AZA.[9,17] One study evaluated the treatment with PRED, PRED+AZA, titrated PRED and placebo or AZA.[18] Another trial studied the same drugs but titrated PRED.[8] One study compared PRED with no intervention.[7] Applied dosages varied between 10-60 mg daily of PRED (maintenance dose 10-20 mg/day)[7-9,17,18] and between 50-100 mg daily of AZA.[8,9,17,18]

Ninety-five patients were treated with PRED (not titrated), remission occurred in 42%.[8,17,18] We were not able to extract remission rates in two studies, as they contained only minimal information.[7,9] The mortality rate was 15% (21/139) (Figure 2a).[7-9,17,18]

Only 14% of 51 AZA treated patients achieved remission,[8,17] and 30% deceased (27/89).[8,9,17,18] The therapy of PRED+AZA in 44 patients yielded a remission rate of 43% and a mortality rate of 7%.[8,18] Remission rates of PRED treated patients versus PRED+AZA treated patients yielded a comparable rate (RR=0.98; 95%CI 0.65-1.47). Neither of 33 patients randomized for placebo achieved remission, and 13 patients (39%) died.[8,18] One study assessed 27 patients with no

intervention, the remission rate could not be extracted and the mortality rate was 56%.[7] One study evaluating the effect of titrated PRED showed no benefit.[18]

Figure 1. Flowchart of included and excluded articles in the systematic literature search

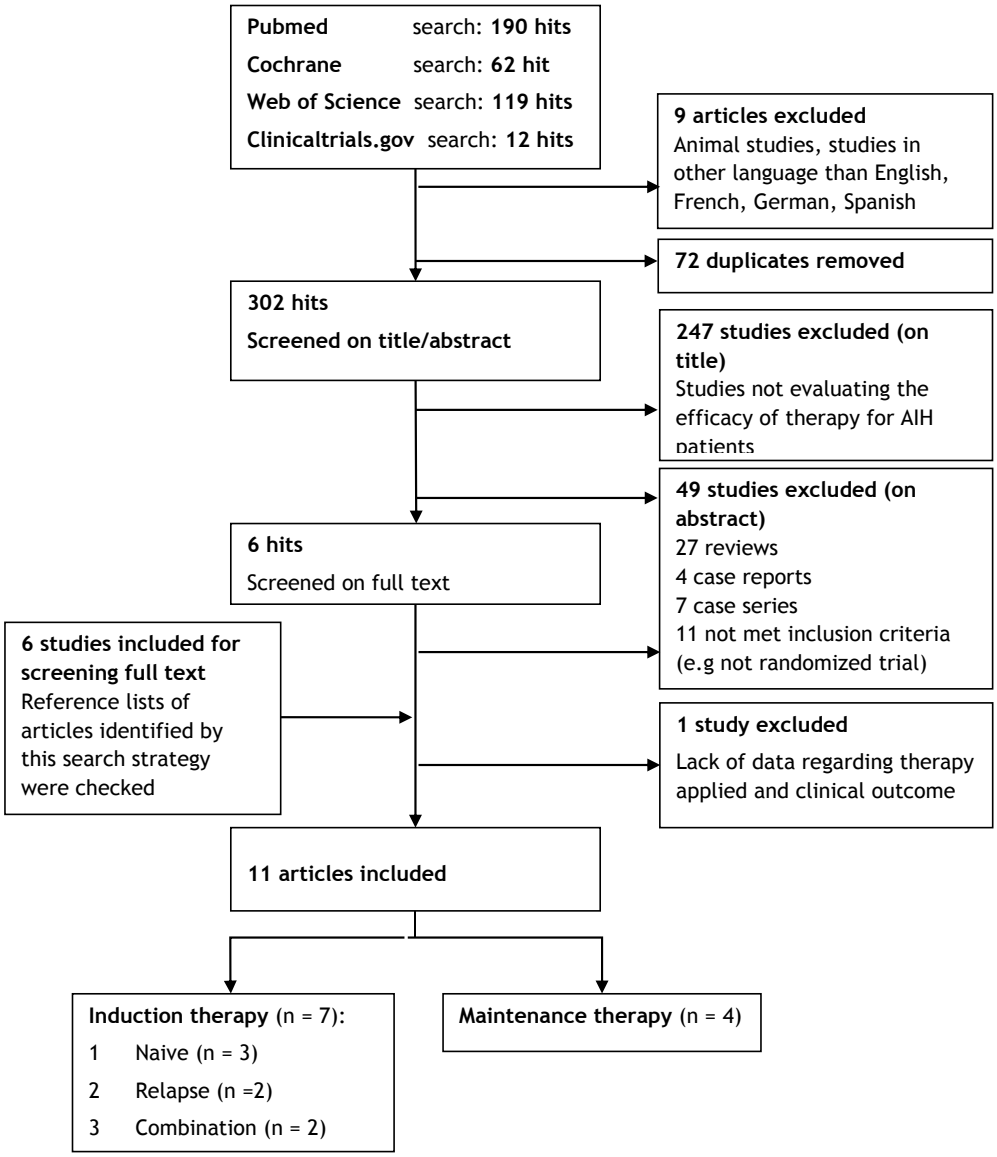
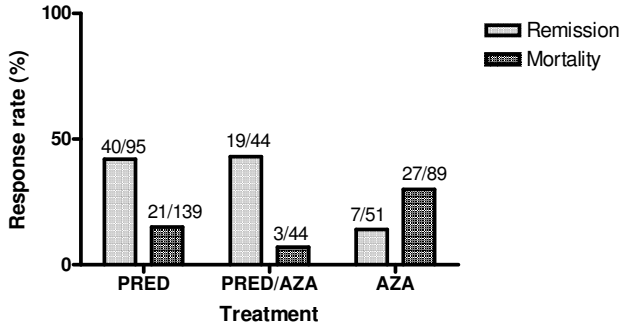


Figure 2a: Induction therapy naive AIH patients



Induction therapy in AIH patients who relapsed

Four studies, with a Jadad score between 2 and 4, assessed the clinical outcome of induction therapy in AIH patients who relapsed (Table 2).[8,9,14,15] In total, these 4 studies included 163 patients (22% males) in 7 different arms. The most important comparators were similar to the studies in naive patients: PRED (15-60 mg/day) versus AZA (75-100 mg/day) or a combination of these two (PRED 10-30 mg/day, AZA 50 mg/day) versus monotherapy.[8,9,15] One study compared ursodeoxycholic acid (UDCA 13-15 mg/kg/day) with placebo in PRED treated patients, and UDCA showed no additional value.[14] A total of 32% from 34 PRED treated patients obtained remission,[8,14] 4% died (Figure 2b).[8,9,14] Twenty-two patients treated with PRED+AZA achieved remission in 45% and had a corresponding mortality of 5%.[8,15] Treatment with PRED or with PRED+AZA were not different (RR=0.71; 95%CI 0.37-1.39). Two studies focused on AZA treatment.[8,9] Only 7% reached remission [8] and 28% died.[8,9] For comparison, none of the patients who received placebo came into remission, and there was an associated mortality of 41%.[8]

Figure 2b: Induction therapy relapse AIH patients

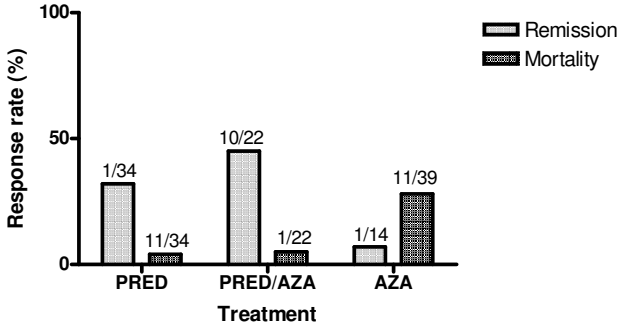


Table 1. Induction therapy in naive patients with autoimmune hepatitis

First author, journal, year	Intervention	Treatment duration	Patients (n)	Remission (%)	Mortality (%)	Jadad score
Cook, Quarterly Journal of Medicine, 1971	Prednisolone 15 mg/day	30-72 months	22	-	14	2
	No intervention		27	-	56	
Soloway, Gastroente-rology, 1972	Prednisone 60 mg/day 1 week, 40 mg/day 1 week, 30 mg/day 2 weeks, 20 mg/day maintenance	3 months - 3,5 years	18	44	6	4
	Azathioprine 100 mg/day		14	7	36	
	Prednisone 30 mg/day 1 week, 20 mg/day 1 week, 15 mg/day 2 weeks, 10 mg/day maintenance + azathioprine 50 mg/day		14	21	7	
	Placebo		17	0	41	
Murray-Lyon, Lancet, 1973	Prednisone 5mg 3dd	2 years	22	-	5	3
	Azathioprine 75 mg 1dd		25	-	24	
Summerskill, Gut, 1975	Prednisone 60 mg/day 1 week, 40 mg/day 1 week, 30 mg/day 2 weeks, 20 mg/day maintenance	36 months	30	37	10	1
	Prednisone 30 mg/day 1 week, 20 mg/day 1 week, 15 mg/day 2 weeks, 10 mg/day maintenance + azathioprine 50 mg/day		30	53	7	
	Prednisone in doses titrated given on alternated days		31	10	7	
	Placebo/azathioprine 100 mg/day		29 (16/13)	-	41 (38/46)	
Tage-Jensen, Liver, 1982	Azathioprine 10 mg/kg/ week, first 2 weeks 5 mg/ kg/week	38 (12-83) months	37*	16	27	2
	Prednisone <70 kg 10mg/day, ≥70 kg 15mg/day		47*	45	28	

*Ninety-nine autoimmune patients, information provided for 84 patients only. Thirty-four patients prednisone for 1 year, 27 patients azathioprine for 1 year. Thirteen patients who were treated with prednisone died before 1 year of treatment, while 10 patients died in the azathioprine group

Table 2. Induction therapy in patients with autoimmune hepatitis who relapsed

First author, journal, year	Intervention	Treatment duration	Patients (n)	Remission (%)	Mortality (%)	Jadad score
Soloway, Gastroente-rology, 1972	Prednisone 60 mg/day 1 week, 40 mg/day 1 week, 30 mg/day 2 weeks, 20 mg/day maintenance	3 months - 3,5 years	18	44	6	4
	Azathioprine 100 mg/day		14	7	36	
	Prednisone 30 mg/day 1 week, 20 mg/day 1 week, 15 mg/day 2 weeks, 10 mg/day/week + azathioprine 50 mg/day		14	21	7	
	Placebo		17	0	41	
Murray-Lyon, Lancet, 1973	Prednisone 5mg 3dd	2 years	22	-	5	3
	Azathioprine 75 mg 1dd		25	-	24	
Czaja, Hepatology, 1993	Oral pulse prednisone 90 mg/ day for 5 consecutive days, every 28 days	Indefinite	8	0	0	3
	Prednisone 30 mg/day 1 week, 20 mg/day 1 week, 15 mg/day 2 weeks, 10 mg/day/week + azathioprine 50 mg/day		8	88	0	
Czaja, Hepatology, 1999	UDCA 13-15 mg/kg/day + usual corticosteroid schedule	6 months	21	14	5	2
	Placebo + usual corticosteroid schedule		16	19	0	

UDCA = ursodeoxycholic acid

Maintenance therapy in AIH patients

We identified 4 clinical trials that focused on AIH patients in remission on maintenance therapy (Table 3).[12,13,16,19] These studies included 162 patients in 6 different arms, of which 22% were male. Three studies scored 3 on the Jadad scale,[12,13,19] one study scored 1.[16] One study compared AZA (2 mg/kg/day) with PRED (5-12,5 mg/kg/day) + AZA (1 mg/kg/day),[13] another study compared this combination ((PRED 5-10mg/kg/day) + (AZA 50-100 mg/day)) with PRED (5-12,5 mg/day).[12] Two trials compared either thymostimulin with no intervention or PRED (15 mg/day) with D-penicillamine.[16,19] Thymostimulin and D-penicillamine had no relevant clinical value. PRED+AZA yielded a higher rate of maintaining remission (96%)[12,13] than PRED (68%[12,19], RR=1.40; 95%CI 1.13-1.73). A total of 92% of AZA treated patients

maintained remission (Figure 2c)[13]. Maintenance treatment with PRED+AZA is not better than with AZA (RR=1.06; 95%CI 0.94-1.20). AZA also maintained a higher remission rate than PRED (RR=1.35; 95%CI 1.07-1.70). In all studied treatment groups none deceased.[12,13,19]

Figure 2c: Maintenance therapy AIH patients

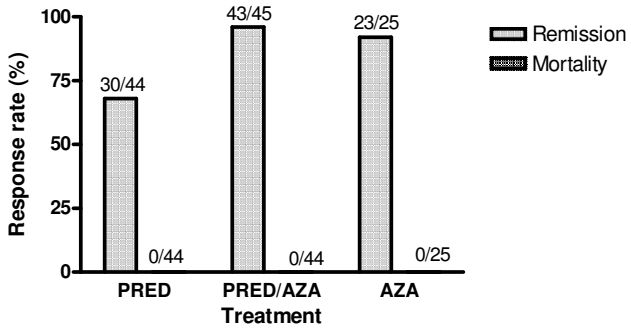


Table 3. Maintenance therapy for autoimmune hepatitis patients in remission

First author, journal, year	Intervention	Treatment duration	Patients (n)	Remission (%)	Mortality (%)	Jadad score
Stern, Gut, 1977	D-penicillamine 1.2 g/day	1 year	18	50	0	3
	Prednisone 15 mg/day		17	65	0	
Hegarty, Gut, 1984	Thymostimulin 1 mg/kg/day i.m. for 7 days; 1 mg/kg/weekly thereafter	Indefinite	13	16	0	1
	No therapy		17	12	0	
Stellon, Lancet, 1985	Prednisolone 5-10 mg/day + Azathioprine 50-100 mg/day	3 years	23	96	0[1]	3
	Prednisolone 5-12,5 mg/day		27	70	0[1]	
Stellon, Hepatology, 1988	Azathioprine 2 mg/kg/day	1 year	25	92	0	3
	Azathioprine 1 mg/kg/day + Prednisolone 5-12,5 mg/day		22	100	0	

[1] One patient died in a road accident, inclusion group unknown

Table 4. Adverse events

First author, journal, year	Intervention	Treatment duration	Patients (n)	Adverse events (n)
Cook, Quarterly Journal of Medicine, 1971	Prednisolone 15 mg	Indefinite	22	Severe: osteoprosis + vertebral collapse (2), perforated duodenal ulcer (1), acute steroid psychosis (1), terminal bronchopneumoniae (1). Mild: obesity (5), facial 'mooning' (5), acne (4), myositis (1)
Soloway, Gastroenterology, 1972	Prednisone 60 mg/day 1 week, reduction schedule to 20 mg/day maintenance	3 months - 3,5 years	18	Cushingoid appearance (13), diabetes requiring insulin (1), GI-bleeding (1), spinal collapse, aseptic necrosis of hip, or cataracts (3)
Murray-Lyon, Lancet, 1973	Prednisone 5mg 3 times a day	2 years	22	-
Summerskill, Gut, 1975	Prednisone 60 mg/day 1 week, reduction schedule to 20 mg/day maintenance	36 months	30	Severe cosmetic changes, diabetic mellitus cataracts, hypertension
Summerskill, Gut, 1975	Prednisone in doses titrated given on alternated days	36 months	31	Diabetes mellitus, diabetes mellitus and hypertension, hematemesis/melena
Tage-Jensen, Liver, 1982	Prednisone <70 kg 10mg/day, ≥70 kg 15mg/day	38 (12-83) months	47	-
Stellon, Lancet, 1985	Prednisolone 5-12,5 mg/day	3 years	27	-
Czaja, Hepatology, 1993	Oral pulse prednisone 90 mg/day for 5 consecutive days, every 28 days	Indefinite	8	None
Soloway, Gastroenterology, 1972	Prednisone 30 mg/ day 1 wk, reduction schedule to 10 mg/day/wk + azathioprine 50 mg/day	3 months - 3,5 years	14	Cushingoid appearance (10)
Summerskill, Gut, 1975	Prednisone 30 mg/ day 1 wk, reduction schedule to 10 mg/day/wk + azathioprine 50 mg/day	36 months	30	Diabetes mellitus, hematemesis;

Stellon, Lancet, 1985	Prednisolone 5-10 mg/day + azathioprine 50-100 mg/day	3 years	23	None
Stellon, Hepatology, 1988	Prednisolone (5-12,5 mg/day) + azathioprine 1 mg/kg/day	1 year	22	Arthralgias (1)
Czaja, Hepatology, 1993	Prednisone 60 mg/day 1 week, reduction schedule to 20 mg/day maintenance	Indefinite	8	Severe adverse events of azathioprine not observed
Soloway, Gastroenterology, 1972	Azathioprine 100 mg/day	3 months - 3,5 years	14	Cushingoid appearance (2), GI-bleeding (3), spinal collapse, aseptic necrosis of hip, or cataracts (1), leucopenia/ trombopenia (2), ascites + 2x increase in bilirubin (>6mg/100ml) (2)
Murray-Lyon, Lancet, 1973	Azathioprine 75 mg once daily	2 years	25	-
Summerskill, Gut, 1975	Azathioprine 100 mg/day	36 months	13	-
Tage-Jensen, Liver, 1982	Azathioprine 10 mg/kg/week, first 2 weeks 5 mg/kg/week	38 (12-83) months	37	-
Stellon, Hepatology, 1988	Azathioprine 2 mg/kg/day	1 year	25	Arthralgia most hinged joints (14), myalgias (7), transient leucopenia (1), pancytopenia (2)

Adverse events

Frequencies and percentages of reported adverse events were not adequately mentioned in most studies. Patients receiving PRED had a number of well-known steroid related adverse events such as cushingoid appearance, diabetes mellitus, hypertension and cataracts (Table 4). Adverse events associated with AZA treatment were gastrointestinal bleeding, leucopenia, trombopenia, and arthralgia. Cushingoid appearance and diabetes mellitus were adverse events associated with the combination therapy PRED+AZA, but in a lower reported frequency than PRED monotherapy. We found no differences in adverse event incidence between treatment indications (naive, relapse or remission).

Discussion

This systematic review evaluates the evidence that is available for induction and maintenance therapy in AIH. Results from our analysis show that both PRED monotherapy and PRED+AZA are better in achieving remission and limiting mortality in treatment naive AIH patients than any other treatment option evaluated in the literature between 1950 and July 2009. The efficacy of both strategies seems similar, and the lower mortality rate with PRED or PRED+AZA is an important additional argument to favor this therapy over AZA monotherapy for the initial treatment of both naive and relapsing patients.

For patients who require maintenance therapy, the combination PRED+AZA and AZA monotherapy provides higher maintenance rates of persistent remission compared to PRED monotherapy. Testament to this is that mortality was absent with either choice. Although AIH is much more prevalent in females, we could not discern a gender difference in efficacy for either naives, relapsers or patients in remission.

Surprisingly, the number of RCTs describing the clinical efficacy of different treatment strategies in AIH patients is low. We only found 11 RCTs published between 1950 and July 2009. For comparison, between July 2008 and July 2009 alone, already around 150 clinical trials in hepatitis C were reported in the literature. Moreover, studies were heterogeneous, performed decades apart with an evolving set of diagnostic criteria and no proper evidence based definition for remission until 1999. In order to offer recommendations for optimal induction and maintenance treatment in AIH we performed a descriptive analysis of the published RCTs.

The question is whether we need future RCTs with currently available treatment options in AIH. We believe that there is a large unmet need. The trials that established the current standard PRED+AZA stem from an era with different, and currently considered suboptimal, laboratory diagnostics. In addition, the epidemiology of AIH probably has shifted. Due to improved diagnostics AIH is probably diagnosed in a much earlier phase, and patients that were considered to have AIH at the time of the earlier trials will currently receive an alternative diagnosis. Thus, there is a need for trials that reflects and benefits the current AIH patient. This brings us to the design of these future trials. Inclusion of a placebo arm for induction treatment of either naive or relapsing AIH is probably unethical. The remission rates with placebo are poor (<12%) , and earlier trials have shown that this strategy is associated with significant mortality.[7,8,16,18] We concur that the therapy of AIH with PRED with or without AZA is far from ideal, and the search for drugs with a favorable risk-benefit ratio is ongoing.[20] For most of the alternative approaches in the past, the results have been disappointing and

the adverse effects severe.[20] Recently a German study group compared combined budesonide and AZA treatment to PRED+AZA in 208 AIH patients. Note that this trial alone includes ~25% of all AIH patients included in a RCT to date. The primary endpoint of the study was complete remission in absence of typical steroid-induced adverse effects.[21,22] Preliminary results indicate that budesonide is an efficacious alternative to PRED, with a more favourable side effect profile. Less adverse events were experienced compared to the data that we presented here. However, results have only been published in abstract-form and long-term results of budesonide are awaited.

In general, the results from our systematic analysis accord with the current guidelines, which advises PRED or PRED+AZA for naive AIH patients.[1,6,10,20] The combination regimen is the preferred treatment because it is associated with a lower occurrence of corticosteroid-related adverse events than the higher dose PRED regimen (10% vs 44%).[18,20] However in individual patients, therapy is best tailored to the patient's presentation.[20] For adults who have relapsed more than once the AASLD advises to be treated with PRED+AZA therapy, low dose PRED, or AZA only.[10] Current maintenance regimens include PRED+AZA or AZA.[4,10] Many AIH patients who have been in complete remission for at least one year with PRED+AZA can remain in remission with a higher dose of AZA alone.[23] Altogether, we can conclude that our results in all three categories match with the current guidelines.

This review has some limitations. A standardized, universally accepted definition of remission in AIH patients exists since 1999. All articles that are part of this review were published in or prior to 1999, and could consequently not match the overall definition.

Apart from differences in definition of a remission, the trials described in the included articles used various doses for PRED and AZA. Therefore, we were not able to abstract the best dose for the highest remission rates using a systematic review.

Thirdly, variations in medication schemes, outcome measures and validity of trials introduced heterogeneity between included studies. Another limitation is that only 11 RCTs have been published since 1950. The current literature is replete with reviews reflecting personal opinion, but lacks well executed RCTs. In addition, most studies include a small number of patients. Indeed, current therapy guidelines are based on 11 trials with only 607 patients reflecting the perpetual lack of evidence. In the same vein we note that there is also a paucity of structured and systematic recording of adverse events with AIH therapy.

Current literature indicates remission rates of 65-80%[24], but we found much lower percentages. The early RCTs in the 1970's that established the efficacy of corticosteroids in the treatment of AIH included severe cases of AIH with severe, rapidly progressive disease.

Consequently, these studies contained more patients with cirrhosis, which led to worse treatment outcomes and a higher mortality rate. Patients with less severe disease probably have not been included in the controlled clinical trials.[25] Data on mild AIH are missing from the literature, and this introduces a potential source of bias. Furthermore, the hepatitis C virus was identified in 1989.[21] Thus, AIH patients diagnosed prior to 1989 could have hepatitis C, and probably some patients were inadvertently included in the initial trials. This could translate in a lower remission rate. In addition, we did not take into account the lead time bias, which also may affect the achievement of remission and mortality.

In conclusion, PRED monotherapy and PRED+AZA combination therapy are equivalent in efficacy for induction treatment in naive and relapsing AIH patients. For maintenance therapy PRED+AZA combination and AZA monotherapy are superior to PRED monotherapy. Alternative proposed strategies in patients who have failed to achieve remission on standard therapy or patients with drug toxicity are very welcome to optimize treatment.

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B Hepatitis Delta

3

Interferon-alpha for patients with chronic hepatitis delta; a systematic review of randomized clinical trials

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Abstract

Background: Hepatitis delta virus (HDV) infection therapy is unclear.

Aim: This systematic analysis aims to clarify the evidence on the efficacy of interferon alpha (IFNα) based therapy in HDV.

Methods: We performed a systematic search on electronic databases MEDLINE (1970-01.2011), Web of Science, Cochrane and the website www.clinicaltrials.gov. RCTs comparing IFNα based therapy with either another drug, placebo or no intervention were included. We excluded pediatric studies. We calculated relative risks (RR) for comparison of treatment options on the primary outcome measure, which was defined as undetectable levels of HDV RNA and normal ALT at end of treatment (EOT=1-year).

Results: Nine randomized clinical trials (RCTs) were included. Seven trials evaluated the treatment with IFNα (n=132). The remaining 2 trials evaluated treatment with pegylated IFNα (peg-IFNα) (n=45). We found that 1-year treatment with high-dose-IFNα achieved better primary outcome rates than with peg-IFNα (RR=4.14; 95%CI 1.00-17.14). One year treatment with low-dose-IFNα or with peg-IFNα were similar (RR=2.83; 95%CI 0.65-12.40) as were low-dose-IFNα and high-dose-IFNα (RR=0.68; 95%CI 0.31-1.50). High-dose-IFNα and peg-IFNα reached similar HDV RNA suppression 24 weeks after EOT (RR=1.00; 95%CI 0.51-1.97). None of the 55 patients assigned to no intervention obtained undetectable levels of HDV RNA and only one patient achieved normalization of ALT level.

Conclusions: Based on available RCTs 1-year high-dose-IFNα monotherapy appears to be more effective than peg-IFNα for treatment of HDV patients, with efficacy rates around 30%. There is a lack of head-to-head comparisons. Combination therapies and longer treatment duration needs to be investigated.

Introduction

Hepatitis delta virus (HDV) was first identified in 1977 in serum of hepatitis B surface antigen (HBsAg) carriers.[1] HDV is a parenterally transmitted RNA virus that requires hepatitis B virus (HBV) surface proteins to form the viral coat and to infect hepatocytes. There are 8 genotypes that each have a unique geographical representation.[2-10]

HDV infection occurs as co-infection or superinfection. Co-infection of HBV with HDV is usually acute and self-limiting, with a clinical picture that ranges from mild to severe fulminant hepatitis. Chronic liver disease is seen in less than 5% of these patients.[11, 12] Superinfection of HDV in HBV carriers is associated with severe acute hepatitis that leads to chronic HDV infection in up to 80% of patients.[11-16] All in all, an estimated 10% of chronic HBV infected patients have a concomitant HDV infection, with considerable differences between countries, regions and risk groups.[12, 17] Eventually, this may lead to chronic liver disease and progression to cirrhosis in 80% of patients.[13, 15, 16, 18-21]

Treatment of chronic HDV remains under debate. Clinical trials dating from the mid-1980s and beginning 1990s used interferon alpha (IFNα) based therapy to inhibit HDV replication.[22-27] Response with IFNα was not high, but therapeutic efficacy seemed to increase with higher IFNα dosages [28, 29] and prolonged therapy.[22, 23, 30, 31] The addition of polyethylene glycol to IFNα, which enhances the half-life of IFNα, greatly increased the therapeutic efficacy in hepatitis C.[32-34] The effect of pegylated IFNα (peg-IFNα) in HDV treatment has not been fully explored.[35, 36] In addition, several oral agents have been proven to be ineffective in HDV, including ribavirin, famcyclovir, lamivudine, levamisole and thymosin.[37-42] Since there is an important therapeutic role of IFNα therapy in the treatment of HDV, an in depth reassessment of the evidence that supports safety and efficacy of IFNα based strategies in HDV is warranted.

Our primary objective was to explore the published literature and clarify the evidence on the effects of IFNα in HDV. Therefore we performed a systematic review and examined all randomized clinical trials (RCTs) for IFNα based treatment of HDV from 1970 until present.

Methods

Literature search

We performed a systematic literature search using a set of electronic databases: PUBMED (from 1970 to January 2011), Web of Science, The Cochrane Library and the website www.clinicaltrials.gov. We identified all published articles, abstracts, and ongoing studies in all languages from 1970 until January 2011. Searches were performed by using the official Medical Subject Headings (MeSH): 'hepatitis', 'HDV', 'delta' and 'clinical trial'. Additional articles were obtained through citation snowballing to locate primary sources that were referred to in the initial document where necessary.

Selection of studies

We included all articles irrespective of language. We included any study that met the following criteria: 1) RCT; 2) comparing IFNα based therapy with another drug, placebo, or no intervention; 3) outcome measures include levels of HDV RNA and alanine aminotransferase (ALT); and 4) treatment duration of 1 year or more. All duplicates and pediatric trials were removed. Subsequently, we screened all remaining articles on the basis of title and abstract. Studies not evaluating the treatment of chronic HDV were removed from the analysis. Case series, cross-sectional studies, cohort studies, review articles and letters were excluded. Thereafter, we subjected the remaining studies to full text screening.

Two reviewers (M.L., O.O.) independently evaluated the eligibility of all studies retrieved from the databases on basis of the predetermined selection criteria. Disagreements were resolved by discussion with a third party (J.D.). In order to determine whether our search included all published articles, we manually searched the reference sections of included articles.

Quality of the included studies was assessed, using a domain-based evaluation, where critical assessments are made separately for different domains.[43]

Outcomes

The primary outcome measure was: 1) undetectable levels of HDV RNA plus 2) normal levels of ALT, both at end of treatment (EOT = 1-year of treatment).

The secondary outcome measures included undetectable levels of HDV RNA at EOT, normal levels of ALT at EOT, both variables at 24 weeks after EOT, mortality, and occurrence of

adverse events. All outcomes were extracted from the included trials and assessed at maximum follow-up.

Data abstraction

We developed an electronic data extraction form in MS Excel and used this for data entry. Extracted data included characteristics of trials, patients and interventions, as well as all outcome measures. Trial characteristics comprised the first author's name, year and journal of publication, study design, type, dose and duration of applied therapy and length of follow-up. Patient characteristics included inclusion and exclusion criteria, mean age, number of patients randomized, number of and reasons for dropouts and withdrawals.

Synthesis of data and analysis

For each separate study, a brief overview of the interventions and number of patients was generated. We pooled patient data from all studies and stratified results in different subgroups according to applied intervention. Thereafter, we determined the primary and secondary outcome measures to assess the efficacy of the different applied interventions. We calculated relative risks (RR) for comparison of treatment options on the primary and secondary outcome measures.

Results

Literature search and selection of studies

The search of our systematic literature search and subsequent selection of articles is summarized in a flow diagram (figure 1). The initial search identified 419 different articles. We excluded 356 articles on basis of different study aims and 48 papers were rejected because the study design did not meet the inclusion criteria. Full text screening was applied for 15 articles and ultimately 8 full papers met the selection criteria. We checked the reference lists of the first set of 8 articles, and this strategy resulted in one additional article. Thus, a total of 9 RCTs were included for further analysis.[23, 28, 29, 31, 36, 38, 44-46] Seven studies evaluated the treatment with IFNα (n = 132 patients monotherapy)[23, 28, 29, 31, 38, 44, 45] and another 2 studies evaluated treatment with peg-IFNα (n = 45 patients monotherapy).[36, 46]

The RCTs evaluated IFNα based therapies in combination with lamivudine, ribavirin, and adefovir. Outcome assessments in patients treated within the different treatment arms were

made after an evaluation period of ≥1 year. The mean evaluation period was comparable between the different groups, approximately 1 year, except for one article that had a 2 year evaluation phase. Most trials used a 6-month follow-up period.

Interferon alpha based monotherapy

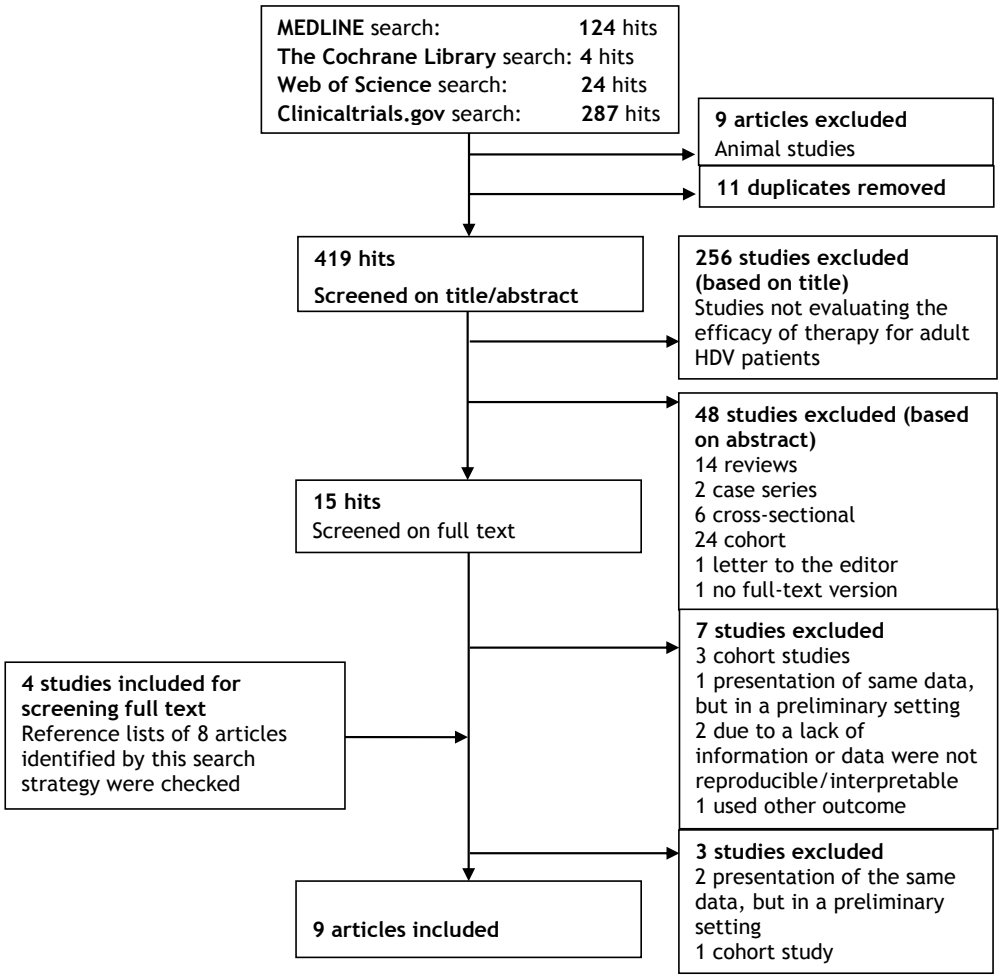
We retrieved 7 studies, published between 1991 and 2008 which assessed our primary outcome of 1-year IFNα therapy in chronic HDV patients. These 7 trials evaluated 253 patients allocated to 7 different intervention groups and 73% of participants were male (Table 1).[23, 28, 29, 31, 38, 44, 45] Two studies compared IFNα, in different dosages ranging from 5 MU/m2 three times in a week (t.i.w.) to 10 MU/m2 twice a week, without a comparator.[23, 31] Two studies performed a head-to-head comparison between high (9 MU t.i.w. or 18 MU t.i.w.) and low dose (3 MU t.i.w. or 3 MU daily) IFNα, while a single study used a non-treated control group.[28, 29] One study compared IFNα monotherapy (10 MU t.i.w.) with combination therapy of IFNα (10 MU t.i.w.) and lamivudine (100 mg daily).[44] Another trial studied the same drugs (IFNα therapy (9 MU t.i.w.), combination therapy of IFNα (9 MU t.i.w.) with lamivudine (100 mg daily)) but included a third arm with lamivudine monotherapy (100 mg daily).[38] One study performed a comparison between IFNα monotherapy (9 MU t.i.w.) and IFNα (9 MU t.i.w.) and ribavirin (1000-1200 mg daily) combination therapy.[45]

We identified two clinical trials that investigated the efficacy of peg-IFNα therapy in chronic HDV patients (Table 2).[36, 46] These studies included 128 patients (62% male) allocated to 4 different intervention groups.[36, 46] The first study compared peg-IFNα (1.5 µg/kg/week) with peg-IFNα (1.5 µg/kg/week) in combination with ribavirin (800 mg daily).[46] The second study evaluated peg-IFNα (180 µg/week) and adefovir (10 mg daily) combination therapy, the combination of peg-IFNα (180 µg/week) and placebo, and adefovir monotherapy (10 mg daily).[36]

Primary outcome measure: One-hundred-twenty-two patients were treated with IFNα for 1-year [23, 28, 29, 31, 38, 44], 72 patients were treated with low dose (3-5 MU t.i.w.) IFNα.[23, 28, 29, 31] The combination of undetectable levels of HDV RNA and normal levels of ALT at EOT (1-year treatment) was observed in 20% of patients (figure 2).[28, 29, 31] We were not able to extract data on the primary outcome measure from one study as this manuscript contained only minimal information.[23]

Twenty-nine percent of high dose (9-18 MU t.i.w.) IFNα treated patients (n=42) reached both undetectable HDV RNA and normal ALT levels.[28, 29, 44] Patients on low dose IFNα had a similar response compared with high dose IFNα (RR = 0.68; 95% CI 0.31-1.50).

Figure 1. Flowchart of included and excluded articles in the systematic literature search



Forty-five patients were treated with peg-IFNα.[36, 46] Only 7% reached combined undetectable levels of HDV RNA and normal levels of ALT at EOT.[36] One year treatment with low dose IFNα or with peg-IFNα was not significantly different (RR = 2.83; 95% CI 0.65-12.4). One year treatment with high dose IFNα was better compared to peg-IFNα (RR = 4.14; 95% CI 1.00-17.14).

Secondary outcome measures: Sixteen of 72 patients (22%) treated with low dose IFNα reached undetectable levels of HDV RNA at EOT.[23, 28, 29, 31] Similarly, 22% of peg-IFNα treated patients (n=45) achieved HDV RNA negativity.[36, 46] Forty-eight percent of 50 high dose IFNα treated patients attained undetectable levels of HDV RNA.[28, 29, 38, 44] High dose IFNα was

more effective than low dose IFNα or peg-IFNα to achieve undetectable HDV RNA (RR = 2.16; 95% CI 1.28-3.63 / RR = 2.16; 95% CI 1.16-4.01). There was no significant difference between low dose IFNα or peg-IFNα (RR = 1.00; 95% CI 0.50-2.01).

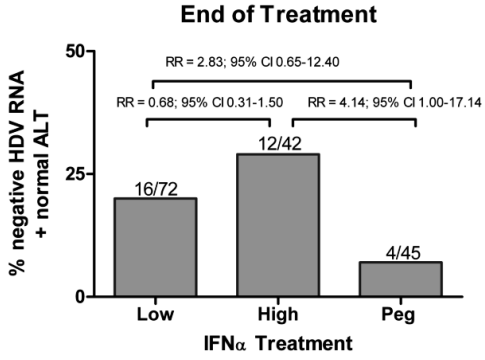
Table 1. Interferon alpha therapy in HDV patients

First author, journal, year	Intervention	Treatment duration (years)	Patients (n)	Undetectable levels of HDV RNA & normal levels of ALT (%)	Undetectable levels of HDV RNA (%)	Normal levels of ALT (%)
Rosina Hepatology 1991 [23]	**Rec IFNα-2b** 3x/w 5 MU/m² 4 months 3 MU/m² 8 months	1	31	Unknown	0	26
	No intervention		30	Unknown	0	0
Farci NEJM 1994 [28]	**Rec IFNα-2a** 9 MU 3x/w	1	14	50	71	71
	Rec IFNα-2a 3 MU 3x/w		14	21	36	29
	No intervention		14	0	0	8
Madejon Hepatology 1994 [29]	3MU **rec IFN**/day 3 months; 1.5MU/ day for 9 months	1	16	6	25	12
	18 MU of **rec IFN** 3x/w 6 months,9 MU 3x/w 1 month, 6 MU 3x/w 1 month, 3 MU 3x/w 4 months		16	6	31	31
Gaudin Liver 1995 [31]	**IFNα-2b**; 5 MU 3x/w 4 months, 3 MU 3x/w 8 months	1	11	36	64	36
	No intervention		11	0	0	0
Gunsar Antiviral Therapy 2005 [44]	**IFNα-2a** 9 MU 3x/w 2 years	2	10	50	50	50
	IFNα-2a 9 MU 3x/w + **Ribavirin** 1000-1200 mg/day		21	unknown	52	57

Canbakan Gastroenterol & Hepatology 2006 [45]	**IFNα-2b** 10 MU 3x/w	1	12	33	42	42
	IFNα-2b 10 MU 3x/w + **Lamivudine** 100 mg/day		14	50	64	57
Yurdaydın Viral Hepatitis 2008 [38]	**Lamivudine** 100 mg 1dd[a]	1	9	Unknown	11	22
	IFNα-2a 9 MU 3x/w[a]		8	Unknown	50	63
	Lamivudine (2 months alone, 100 mg 1dd) + **Lamivudine and IFNα-2a** 10 months[a]		8	Unknown	50	75
	Lamivudine 100 mg 1dd[b]		8	Unknown	13	13
	Lamivudine (2 months alone, 100 mg 1dd) + **Lamivudine and IFNα-2a** 10 months[b]		6	Unknown	50	50

a Treatment-naive patients (n=25). b Previously treated with interferon (IFN; n=14). ALT, alanine aminotransferase; IFNα, interferon alpha; HDV, hepatitis delta virus; 3x/w, three times a week; MU, million units; 1dd, once daily

Figure 2: HDV RNA negativity and normal alanine aminotransferase at end of treatment



The comparison of high-dose IFNα versus PEG-IFNα was clinically significant. Values above bars represent comparisons between the treatment groups with associated risk ratios.

ALT, alanine aminotransferase; HDV, hepatitis delta virus; PEG-IFNα, pegylated interferon alpha
virus; RR, relative risk

Table 2. Peg interferon alpha therapy in HDV patients

First author, journal, year	Intervention	Treatment duration (years)	Patients (n)	Undetectable levels of HDV RNA & normal levels of ALT (%)	Undetectable levels of HDV RNA (%)	Normal levels of ALT (%)
Niro Hepatology 2006 [46]	**Peg-IFNα**-2b 1.5µg/kg/week	1½	16	Unknown	19	37
	Peg-IFNα-2b 1.5µg/kg/week + **Ribavirin**; 800 mg/day 48 weeks; **Peg-IFNα-2b** 24 weeks monotherapy		22	Unknown	9	41
Wedemeyer NEJM 2011 [36]	**Peg-IFNα**-2a 180 µg/week + **Adefovir** 10 mg daily	1	31	7	23	32
	Peg-IFNα-2a 180 µg/week + Placebo		29	7	24	28
	Adefovir 10 mg daily		30	0	0	7

Treatment with low dose IFNα resulted in normal levels of ALT in 25% of 72 patients.[23, 28, 29, 31] Normalization of ALT was reached in 25 of 50 high dose IFNα treated patients.[28, 29, 38, 44] Thirty-one percent of 45 patients achieved normal ALT levels with peg-IFNα.[36, 46] High dose IFNα was more effective in reaching normal levels of ALT than low dose IFNα (RR = 2.00; 95% CI 1.23-3.25). Furthermore, the efficacy of low and high dose IFNα was not different from that of peg-IFNα (RR = 0.80; 95% CI 0.45-1.45 / RR = 1.61; 95% CI 0.96-2.69).

Because none of the manuscripts contained information on the primary outcome measure after EOT (for example at 24 weeks after EOT) we were not able to extract these data. Four of the 72 patients (6%) treated with low dose IFNα had undetectable HDV RNA 24 weeks after EOT.[23, 28, 29, 31] Twenty-nine percent of 38 high dose IFNα treated patients maintained undetectable levels of HDV RNA at follow-up week 24.[28, 29, 38] Thirteen of 45 peg-IFNα treated patients (29%) achieved negative HDV RNA levels.[36, 46] High dose IFNα and peg-IFNα were better than low dose IFNα in reaching undetectable HDV RNA 24 weeks after EOT (RR = 6.00; 95% CI 0.06-0.49 / RR = 5.99; 95% CI 2.08-17.31). High dose IFNα and peg-IFNα were similarly effective (RR = 1.00; 95% CI 0.51-1.97).

Normal ALT levels 24 weeks after EOT were achieved in 6% of 72 patients treated with low dose IFNα.[23, 28, 29, 31] Moreover, 32% of 38 high dose IFNα and 38% of 45 peg-IFNα treated patients reached normal levels of ALT.[28, 29, 36, 38, 46] High dose IFNα and peg-IFNα were more successful in obtaining normal ALT levels than low dose IFNα at 24 weeks after EOT (RR = 5.68; 95% CI 1.97-16.43 / RR = 6.8; 95% CI 2.44-18.92). High dose IFNα and peg-IFNα were similarly effective in this respect (RR = 0.84; 95% CI 0.49-1.52).

For comparison, none of the 55 patients who received placebo or no intervention obtained undetectable levels of HDV RNA and ALT levels normalized only in a single patient. There was no mortality in patients assigned to no intervention.[23, 28, 31] This contrasts with one patient in the high dose IFNα group who died due to liver decompensation in the 5th month of therapy[44] and one patient in the low dose IFNα group who committed suicide.[31]

Five of the 10 patients who were treated for 2 years with high dose IFNα reached undetectable HDV RNA and normal ALT levels. One patient obtained normal ALT, but failed to reach undetectable HDV RNA.[45] IFNα treatment for 1-year or 2 years was not different (RR = 0.45; 95%CI 0.17-1.22). The article describing the trial gave no information on mortality.[45]

IFN alpha based combination therapy and other monotherapies

A total of 57% of 28 patients on IFNα and lamivudine reached undetectable levels of HDV RNA [38, 44], 61% achieved normalization of ALT levels [38, 44], and 50% attained both.[44] IFNα monotherapy and IFNα in combination with lamivudine were similarly effective (RR = 0.45; 95%CI 0.19-1.07). Lamivudine monotherapy was investigated in 17 patients. Undetectable HDV RNA was seen in 12%, while 18% reached normal ALT levels.[38]

One trial studied the combination of IFNα and ribavirin for 2 years. Fifty-two percent of 21 patients achieved undetectable HDV RNA levels and 57% reached normal ALT levels.[45] Peg-IFNα in combination with ribavirin resulted in undetectable HDV RNA levels in 9% (2/22 patients) and in 9/41 patients (41%) normal levels of ALT were obtained.[46] Thirty-one patients were treated with peg-IFNα and adefovir, 23% achieved undetectable levels of HDV RNA, 32% reached normalization of ALT levels and 7% reached both outcome measures.[36] Treatment with peg-IFNα or combination therapy with peg-IFNα and adefovir was not different (RR = 1.07; 95%CI 0.16 – 7.10). Thirty patients were treated with adefovir monotherapy, 7% reached normal ALT levels, none obtained undetectable HDV RNA levels.[36]

Adverse events

Frequencies and percentages of reported adverse events were not always adequately documented. Patients receiving IFNα based therapy had a number of well-known adverse

events such as flu-like syndrome, leucopenia, thrombocytopenia and fatigue (Table 3). We found no differences in adverse events incidence between the different IFNα based therapies. Both in the low dose [23, 28, 29, 31] and high dose IFNα group [28, 29, 38, 44] one patient died. None of the patients treated with peg-IFNα [36, 46] or who received no intervention deceased.[23, 28, 31]

Table 3. Adverse events

First author journal year	Intervention	Treatment duration (years)	Patients (n)	Adverse events (n)
Rosina Hepatology 1991	**Rec IFNα-2b** 3x/w, 5 MU/m² 4 months, 3 MU/m² 8 months	1	31	Flu-like symptoms (31), fatigue (31), weight loss (31), alopecia (6), nausea and anorexia (4), vomiting (2), impaired consciousness (1), rhinorrhea (1), ulcer at the injection site (1), acute icteric hepatitis (1)
Farci NEJM 1994	**Rec IFNα-2a** 9 MU 3x/w	1	14	Flu-like symptoms, asthenia (10), alopecia (8), anemia (1)
Farci NEJM 1994	**Rec IFNα-2a** 3 MU 3x/w	1	14	Flu-like symptoms, asthenia (4) , alopecia (4)
Madejon Hepatology 1994	3MU **rec IFN**/day 3 months; 1.5MU/day for 9 months	1	16	Asthenia (7), anorexia (7), fever (5), weight loss (6), arthralgias (5), hair loss (4), headache (5), itching (2)
Madejon Hepatology 1994	18MU of **rec IFN** 3x/w 6 months, 9MU 3x/w 1 month, 6MU 3x/w 1 month, 3MU 3x/w 4 months	1	16	Asthenia (11), anorexia (9), fever (10), weight loss (9), arthralgias (8), hair loss (8), headache (7), itching (2)
Gaudin Liver 1995	**IFN α-2b** 5MU 3x/w 4 months, 3MU 3x/w 8 months	1	11	Flu-like syndrome(11), hyperthyroidism (1), death by suicide (1), attempted suicide (1), leucopenia, thrombocytopenia
Gunsar Antiviral Therapy 2005	**IFNα-2a** 9 MU 3x/w	2	10	Leucopenia (1)
Gunsar	**IFNα-2a** 9 MU 3x/w +	2	21	Leucopenia (3), anemia (2)

Antiviral Therapy 2005	**Ribavirin** 1000-1200 mg/day			
Canbakan Gastroentero logy and Hepatology 2006	**IFNα-2b** 10 MU 3x/w	1	12	Fatigue (5), fever (4), nausea-vomiting (4), abdominal pain (2), myalgia (2), headache (1), Hair loss (2), influenza-like symptoms (1)
Canbakan Gastroentero logy and Hepatology 2006	**IFNα-2b** 10 MU 3x/w + **Lamivudine** 100 mg/day		14	Fatigue (7), fever (4), nausea-vomiting (3), abdominal pain (2), myalgia (1), headache (1), depression (1), influenza-like symptoms (1)
Yurdaydın Viral Hepatitis 2008	naive patients (25) previously used IFN (14)	1	25 14	Not mentioned
Niro Hepatology 2006	**Peg-IFNα-2b** 1.5 µg/ kg/week	1½	16	Thrombocytopenia (6), neutropenia (2), fatigue, headache, insomnia and irritability, arthralgia, cellulitis, urinary and respiratory infections, nausea, injection site reactions, depression
Niro Hepatology 2006	**Peg-IFNα-2b** 1,5µg/kg/ week + **Riba-virin**; 800 mg/ day 48 weeks; **Peg-IFNα-2b** 24 weeks monotherapy	1½	22	Thrombocytopenia (7) , neutropenia (6), anemia (4), gammaglutamyltransferase elevation (1) fatigue, headache, insomnia and irritability, arthralgia, cellulitis, urinary and respiratory infections, generalized itching, nausea, injection site reactions, depression
Wedemeyer NEJM 2011	**Peg-IFNα-2a** 180 µg/week + **adefovir** 10 mg daily	1	31	Loss of appetite (3), influenza-like symptoms (6), fatigue (8), pyrexia (6), sexual (2), headache (8), cough (3), nausea (3), abdominal pain (7), pruritus (2), rash or rashlike event (8), hair loss (6), psychiatric (2), insomnia (2), myalgia (7), arthralgia (4), neutropenia (3), thrombocytopenia (5)
Wedemeyer NEJM 2011	**Peg-IFNα-2a** 180 µg/week + placebo	1	29	Loss of appetite (3), influenza-like symptoms (2), fatigue (8), pyrexia (2), dry mouth (6), sexual (1), headache (9), dizziness (1), cough (3), nausea (4), abdominal pain (7), pruritus (4), rash or rashlike event (3), hair loss (2), psychiatric (5), insomnia (4), myalgia (8),

				arthralgia (6), neutropenia (2), thrombocytopenia(2)
Wedemeyer NEJM 2011	**Adefovir** 10 mg daily	1	30	Loss of appetite (3), influenza-like symptoms (3), fatigue (4), headache (5), dizziness (3), cough (2), nausea (2), abdominal pain (5), pruritus (2), rash or rashlike event (4), hair loss (1), psychiatric (1), insomnia (1), myalgia (1), arthralgia (1)

Flu-like syndrome = fever, arthralgia, etc.; 3x/w, three times a week; MU, million units

Discussion

In general, we found efficacy rates of 10-30% in achieving both undetectable levels of HDV RNA and normal levels of ALT. These rates indicate that this is an area of clear unmet need. No specific HDV inhibitors have been developed so far. Based on our current knowledge of HDV replication, HBV therapies would be theoretically attractive only if they 1) cleared HBV entirely or 2) reduced levels of HBsAg, on which HDV depends.

The use of HBV inhibitors in HDV has been disappointing and these drugs appear to have no or little effect on HDV replication.[48] Combination of IFNα with nucleoside or nucleotide analogous did not improve virological response rates. However, combination of peg-IFNα and adefovir was superior in reducing quantitative HBsAg levels and induces more often HBsAg seroconversion. As a consequence, combination therapies of peg-IFNα with more potent HBV polymerase inhibitors aiming to induce clearance of both HBsAg and HDV RNA should be explored in HDV.[36]

There is a lack of RCTs in HDV treatment that are useful for the clinician in making evidence based decisions. The number of RCTs describing the clinical efficacy of different treatment strategies in HDV patients is low. We only found 13 RCTs published between 1970 and January 2011. Only 2 of them were RCTs evaluating the efficacy of peg-IFNα.[36, 46] For comparison, between April 2010 and April 2011 alone, already some 20 RCTs in HBV were reported in the literature. An explanation for this difference could be a reduced interest in HDV therapy by pharmaceutical companies because of the relative low burden of HDV infection in western countries.[49-51]

Obviously, new treatment strategies for HDV are needed. Future trials should be powered to detect meaningful differences in the primary outcome, which in this era will be tested with

more reliable and optimal laboratory diagnostics. Furthermore, trials should differentiate between naive and previously treated patients and ideally a long term follow-up is needed to evaluate different treatment outcomes of equal duration.

A new upcoming class of antiviral agents are prenylation inhibitors. These agents block HDAg prenylation, an essential step in the assembly of HDV.[52] Prenylation inhibitors clear HDV from experimental mouse models and are obviously agents that should be tested in a clinical setting.[53] Indeed, clinical trials with these agents have started.[54]

Another issue that requires further investigation concerns the length of treatment. As mentioned, 2 years of IFNα treatment seems better than 1-year.[45] Recently, a Turkish study group retrospectively analyzed standard (<18 months; n = 47) or long term (>18 months; n = 34) conventional or peg-IFNα treatment. The primary endpoint of this study was ALT normalization for at least 6 months post-treatment and undetectable HDV RNA. Preliminary results suggested that standard 1-year course of treatment with IFNα is most likely not enough to achieve ALT normalization in the majority of patients with HDV, and that prolongation of treatment is critical. However, results have only been published in abstract-form.[55] Moreover, in the reviewed trials most patients relapsed after stopping therapy, suggesting that longer treatment might be beneficial.

This review has some limitations. There is no standardized, universally accepted definition of remission in HDV patients. Each described trial used their private end points. For example ALT which was used as end point in all included trials.[23, 28, 29, 31, 36, 38, 44-46] One article described normalization of ALT as 'normalization of ALT levels' [28], whereas another trial described it as 'a decrease of ALT that was greater than or equal to 50% from baseline to a less than 1,5 times the upper limit of normal'.[23] Furthermore, other endpoints of relevance to HDV, such as histological grading and staging, HBV DNA, and HBsAg could not be investigated here. These variables should also be considered in treatment decisions.

One of the most important limitations of this study is the problem with HDV RNA assays. Earlier studies may have used less sensitive HDV RNA assays and thus overestimated virological response rates as compared to more recent trials investigating peg-IFNα.[56] The limit of detection used in the early studies varied between 10 and 100 viral particles per ml [29, 31], compared to 1 to 10 viral particles per ml in the latest studies.[36, 46]

In addition, peg-IFNα may be associated with some increase in ALT levels despite virological response. This phenomenon has been described for HCV infection.[57] Therefore the use of ALT levels as the only outcome measure might underestimate the effect of peg-IFNα.

Another limitation is the short follow-up duration. The majority of studies provided results at EOT and some also at 24 weeks after treatment discontinuation. To be sure that a virologic response is achieved, a longer follow-up would be necessary taking into account that HDV RNA concentrations fluctuate spontaneously.[58]

Furthermore, the trials used various doses of IFNα. Therefore, we were not able to extract the best dose needed for the most optimal response rates. Unfortunately, we were also not able to distinct between naive and treatment experienced patients. There is definitively a need for trials that distinguish between these two categories of patients. Moreover, variations in medication schemes, IFNα based therapy (for example peg-IFNα 2a or 2b), outcome measures, and validity of trials introduced heterogeneity between included studies. Although high dose IFNα seemed more effective than peg-IFNα no formal head-to-head studies have been performed and results are based upon indirect comparisons. In addition, most studies include a small number of patients. Indeed, current therapy is based on 13 trials published since 1970 with only 457 patients, reflecting the paucity of evidence. We also noted some redundancy in the literature. There are a number of articles that report on similar dataset and seem to reuse data from the same patient cohort in subsequent articles.[23, 24, 31, 59, 60] We have excluded these articles from our analysis. In the same context we note that there is also an absence of structured and systematic recording of adverse events in HDV therapy.

In conclusion, one year high dose IFNα monotherapy appears to be more effective than peg-IFNα for treatment of HDV patients. Unfortunately, efficacy rates are only ~ 30% at EOT. Ideally, a long-term follow-up is needed to evaluate different outcomes of equal duration for IFNα and peg-IFNα with the same test used to detect HDV RNA and a comparable long term histological evaluation. Alternative proposed strategies are very welcome to improve the current treatment armamentarium.

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C

Chronic Hepatitis C

4 Aminoadamantanes for chronic hepatitis C

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Abstract

Background: Around 3% of the world's population (approximately 160 million people) are chronically infected with hepatitis C virus. The proportion of infected people who develop clinical symptoms varies between 5% and 40%. Combination therapy with pegylated interferon-alpha plus ribavirin eradicates the virus from the blood six months after treatment (sustained virological response) in approximately 40% to 80% of infected patients, depending on the viral genotype. New antiviral agents, such as boceprevir and telaprevir, in combination with standard therapy, can increase sustained virological response in genotype 1 infected patients to at least 70%. There is therefore an unmet need for drugs that can achieve a higher proportion of sustained virological response. Aminoadamantanes are antiviral drugs used for treatment of patients with chronic hepatitis C.

Objectives: To assess the beneficial and harmful effects of aminoadamantanes for patients with chronic hepatitis C infection by conducting a systematic review with meta-analyses of randomised clinical trials, as well as trial sequential analyses.

Search methods: We conducted electronic searches of the Cochrane Hepato-Biliary Group Controlled Trials Register (1996 to December 2013), the Cochrane Central Register of Controlled Trials (CENTRAL) 2013, Issue 11 of 12 (1995 to December 2013), MEDLINE (1946 to December 2013), EMBASE (1974 to December 2013), Science Citation Index EXPANDED (1900 to December 2013), the WHO International Clinical Trials Registry Platform (www.who.int/ictrp), Google Scholar, and Eudrapharm up to December 2013 and checked the reference lists of identified publications.

Selection criteria: Randomised clinical trials assessing aminoadamantanes in patients with chronic hepatitis C infection.

Data collection and analysis: Two authors independently extracted data. We assessed for risks of systematic errors ('bias') using the 'Risk of bias' tool. We analysed dichotomous data with risk ratio (RR) and continuous data with mean difference (MD) or standardised mean difference (SMD), both with 95% confidence intervals (CI). We used trial sequential analysis to assess the risk of random errors ('play of chance'). We assessed quality using the GRADE system.

Main results: We included 41 randomised clinical trials with 6193 patients with chronic hepatitis C. All trials had high risk of bias. All included trials compared amantadine versus

placebo or no intervention. Standard antiviral therapy was administered equally to the intervention and the control groups in 40 trials. The standard antiviral therapy, which was administered to both intervention groups, was interferon-alpha, interferon-alpha plus ribavirin, and peg interferon-alpha plus ribavirin, depending on the time when the trial was conducted.

When we meta-analysed all trials together, the overall results demonstrated no significant effects of amantadine, when compared with placebo or no intervention, on our all-cause mortality or liver-related morbidity composite outcome (5/2353 (0.2%) versus 6/2264 (0.3%); RR 0.90, 95% CI 0.38 to 2.17; I^2 = 0%; 32 trials; very low quality). There was also no significant effect on adverse events (288/2869 (10%) versus 293/2777 (11%); RR 0.98, 95% CI 0.84 to 1.14; I^2 = 0%; 35 trials; moderate quality). We used both fixed-effect and random-effects meta-analyses. Amantadine, when compared with placebo or no intervention, did not significantly influence the number of patients who failed to achieve a sustained virological response (1821/2861 (64%) versus 1737/2721 (64%); RR 0.98, 95% CI 0.95 to 1.02; I^2 = 35%; 35 trials; moderate quality). However, in the subgroup using interferon plus ribavirin, amantadine decreased the number of patients who failed to achieve a sustained virological response (422/666 (63%) versus 447/628 (71%); RR 0.89, 95% CI 0.83 to 0.96; I^2 = 41%; 11 trials; low quality). Similar results were found for failure to achieve an end of treatment virological response. Amantadine, when compared with placebo or no intervention, significantly decreased the number of patients without normalisation of alanine aminotransferase (ALT) serum levels at the end of treatment (671/1141 (59%) versus 732/1100 (67%); RR 0.88, 95% CI 0.83 to 0.94; I^2 = 47%; 19 trials; low quality). Amantadine, when compared with placebo or no intervention, did not significantly influence the end of follow-up biochemical response (1133/1896 (60%) versus 1151/1848 (62%); RR 0.95, 95% CI 0.91 to 1.00; I^2 = 49%; 21 trials; low quality).

The observed beneficial effects could be true effects but could also be due to both systematic errors (bias) and random errors (play of chance). The latter is due to the fact that trial sequential analyses could not confirm or refute our findings. We were not able to perform meta-analyses for failure of histological improvement or quality of life due to a lack of valid data.

Authors' conclusions: This systematic review does not demonstrate any significant effects of amantadine on all-cause mortality or liver-related morbidity composite outcome and on adverse events in patients with hepatitis C; however, the median trial duration was 12 months, with a median follow-up of six months, which is not long enough to assess the

composite outcome sufficiently. Overall, we did not see an effect of amantadine on failure to achieve a sustained virological response. Subgroup analyses demonstrated that the combination of amantadine plus interferon-alpha and ribavirin seems to increase the number of patients achieving a sustained virological response. This finding may be caused by both systematic errors (bias) and risks of random errors (play of chance), but it could also be real. Based on the results of the overall evidence, it appears less likely that future trials assessing amantadine for patients with chronic hepatitis C will show strong benefits. Therefore, it is probably advisable to wait for the results of trials assessing other direct-acting antiviral drugs. In the absence of convincing evidence of benefit, the use of amantadine is justified in the context of randomised clinical trials assessing the effects of combination therapy. We found a lack of evidence on other aminoadamantanes than amantadine.

Summary of findings

Summary of findings for the main comparison.

Aminoadamantanes compared with placebo or no intervention for hepatitis C					
Patient or population: patients with chronic hepatitis C **Settings:** mainly outpatients in tertiary and teaching hospitals **Intervention:** aminoadamantanes **Comparison:** placebo or no intervention					
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of participants (studies)**	**Quality of the evidence (GRADE)**
	Assumed risk	**Corresponding risk**			
	Placebo or no intervention	**Aminoadamantanes**			
All-cause mortality or liver-related morbidity Follow-up: 12 to 30 months	**Study population**		**RR 0.90** (0.38 to 2.17)	4617 (32 trials)	⊕⊖⊖⊖ **very low** [1]
	3 per 1000	**3 per 1000** (2 to 8)			
Adverse events Follow-up: 12 to 30 months	**Study population**		**RR 0.98** (0.84 to 1.14)	5646 (35 trials)	⊕⊕⊕⊖ **moderate** [2]
	106 per 1000	**101 per 1000** (87 to 118)			
Failure of end of treatment virological response Absence of clearance of HCV RNA from the blood at end of treatment Follow-up: 6 to 12 months	**Study population**		**RR 0.95** (0.90 to 1.00)	4861 (30 trials)	⊕⊕⊕⊖ **moderate** [2]
	534 per 1000	**519 per 1000** (492 to 547)			
Failure of sustained	**Study population**		**RR 0.98** (0.95 to 1.02)	5582 (35 trials)	⊕⊕⊕⊖ **moderate** [2]
	639 per 1000	**637 per 1000** (618 to 663)			

virological response Absence of clearance of HCV RNA from the blood 6 months after treatment Follow-up: 12 to 30 months					
Quality of life Different QoL scales Follow-up: 12 to 30 months	See comment	See comment		1181 (6 trials)	⊕⊖⊖⊖ **very low**[3,4]
Failure of normalisation of ALT at end of treatment Follow-up: 6 to 12 months	**Study population**		**RR 0.88** (0.83 to 0.94)	2241 (19 trials)	⊕⊕⊖⊖ **low**[2]
	666 per 1000	**589 per 1000** (556 to 629)			
Failure of normalisation of ALT at end of follow-up Follow-up: 12 to 30 months	**Study population**		**RR 0.95** (0.91 to 1.00)	3744 (21 trials)	⊕⊕⊖⊖ **low**[2]
	623 per 1000	**598 per 1000** (573 to 630)			

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

ALT: alanine aminotransferase; **CI:** confidence interval; **HCV:** hepatitis C virus; **QoL:** quality of life; **RNA:** ribonucleic acid; **RR:** risk ratio.

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

Background

Description of the condition

Hepatitis C virus was first described in 1989 (Choo 1989). Around 3% of the world's population is affected by chronic hepatitis C infection: on average approximately 160 million people (Sy 2006; Lavanchy 2011). Hepatitis C is a leading cause of liver-related morbidity and mortality, with hepatic fibrosis, end-stage liver cirrhosis, and hepatocellular carcinoma being the dominant clinical sequelae (Sy 2006).

Chronic hepatitis C infection progresses slowly, over a time frame of 15 to 50 years. Both prospective or retrospective studies, following cohorts of patients for decades, suggest that less than 10% of all infected individuals will develop end-stage liver disease. However, there are also publications that have reported on patients who developed cirrhosis two to three decades after infection, with a range of 0.5% to 39% (Koretz 1993; Kenny-Walsh 1999; Rodger 2000; Wiese 2000; Thein 2008; Seeff 2009). The incidence rate of hepatocellular carcinoma is 3 patients per 100,000 person-years in the USA (El-Serag 2003). Hepatitis C is responsible for one-third of hepatocellular carcinomas (El-Serag 2003). In cirrhotic hepatitis C patients, the annual occurrence of hepatocellular carcinoma is 1% to 4% (Lauer 2001). Furthermore, chronic hepatitis C infection is the most common indication for orthotopic liver transplantation (Kim 2009).

Hepatitis C is divided into six genotypes (Simmonds 2005). Genotypes 1 to 4 are the most common (Simmonds 2005). Several factors have an influence on achieving a sustained virological response to antiviral drugs; genotype is one of these factors (Asselah 2010). Genotypes 2 and 3 respond better to antiviral treatment than genotypes 1 and 4 (Asselah 2010).

In 1990, the antiviral drug interferon-alpha was approved for the treatment of chronic hepatitis C as monotherapy (Tine 1991). Interferon-alpha was administered subcutaneously in doses of more than or equal to 3 million units (MU) in the induction phase (over one to three months) and less than 3 MU in the maintenance phase (Tine 1991). Only 10% to 17% of patients achieved sustained virological response, compared to 1% to 3% of the patients receiving no intervention (Davis 1989; Myers 2002).

Antiviral drugs for patients with hepatitis C-related liver disease have improved considerably during the past two decades (Ghany 2009). In 1998, trials assessed the combination of

interferon-alpha and ribavirin (Davis 1998; McHutchison 1998; Poynard 1998). This combination treatment resulted in an improved antiviral response in treatment-naive chronic hepatitis C-infected patients (Brok 2010) and in previously treated patients who had failed to respond to interferon-alpha monotherapy, compared with interferon-alpha alone (Brok 2010).

The success of antiviral therapy has been assessed by 'sustained virological response', that is clearance of hepatitis C ribonucleic acid (RNA) from the blood six months after treatment. Observational studies suggest that people with achieved sustained virological response have less disease progression and lower risk of hepatocellular carcinoma (Ueno 2009). Based on systematic reviews of randomised clinical trials comparing ribavirin plus interferon-alpha versus interferon-alpha alone, the combination of drugs seems to result in more patients with achieved sustained virological response, but we do not know if this results in less mortality or morbidity (Brok 2010). Accordingly, sustained virological response is a non-validated, putative, surrogate outcome measure (Gluud 2007). Furthermore, a recent trial has shown that there is increased mortality in patients who were retreated with interferon-alpha compared with non-treated patients (Di Bisceglie 2011). Other trials cannot confirm or invalidate this finding (Di Martino 2011).

The standard of treatment of chronic hepatitis C infection, according to guidelines, is a combination of pegylated interferon-alpha (peg interferon-alpha) and ribavirin (Ghany 2009; EASL 2011). The regimen can include either peg interferon-alpha-2b (Peg-Intron®, Schering Plough Corp., Kenilworth, NJ) or peg interferon-alpha-2a (Pegasys®, Hoffmann-La Roche, Nutley, NJ), both of which are administered subcutaneously (Awad 2010). The optimal dose of peg interferon-alpha-2b is 1.5 µg/kg/week (Awad 2010). Peg interferon-alpha-2a is administered at a fixed dose of 180 µg weekly (Awad 2010). Ribavirin is administered orally with weight-based total daily doses between 800 mg and 1200 mg (Brok 2009). Some 40% to 80% of chronic hepatitis C patients without co-infection with hepatitis B virus or human immunodeficiency virus (HIV) will achieve a sustained virological response after treatment with peg interferon-alpha and ribavirin (Simin 2007; Awad 2010).

Recently, a new class of drugs for hepatitis C genotype 1 has emerged. These drugs have to be given together with the current standard treatment. They are antiviral agents that inhibit the NS3/N4A serine protease of hepatitis C. This triple therapy can increase sustained virological response proportions to reach 70% to 80% (Bacon 2011; Jacobson 2011; Poordad 2011; Sherman 2011; Zeuzem 2011).

During the 1990s and 2000s, ribavirin was tested as monotherapy for chronic hepatitis C infection (Brok 2009). Ribavirin does not seem to have any major effect on the course of hepatitis C infection (Brok 2009).

Description of the intervention

Aminoadamantanes, such as amantadine and rimantadine, are another antiviral drug group and have also been investigated in several studies for treatment of patients with chronic hepatitis C (Brillanti 1999; Smith 2004). Aminoadamantanes have been investigated as oral monotherapy, administered mostly at a dose of 100 mg twice a day, and also in combination with interferon-alpha or ribavirin, or both. The benefits and harms of amantadine in patients with chronic hepatitis C infection have been explored previously in a meta-analysis (Deltenre 2004). The authors concluded that amantadine therapy had no effect in naive patients or relapsers. However, combination therapy of amantadine with interferon-alpha and ribavirin did improve sustained virological response proportions in non-responder patients.

How the intervention might work

Aminoadamantanes have been used for many years to prevent infection with influenza and have been shown to have activity against *Flaviviridae*, encompassing hepatitis C infection (Koff 1980). Known mechanisms of action of aminoadamantanes include inhibition of an early step in viral replication, most likely viral uncoating and interaction with the influenza A viral matrix protein (M2), which is important in virion budding (De Clercq 2001). The aminoadamantane amantadine acts in a similar way to ribavirin, which in monotherapy often improves liver biochemistry (Reichard 1991; Brok 2009). However, it is unclear whether aminoadamantanes reduce the hepatitis C viral load or improve liver biochemistry (Reichard 1993). Furthermore, it is unclear whether aminoadamantanes affect patient-relevant outcomes.

Why it is important to do this review

The combination therapy of peg interferon-alpha and ribavirin achieves virus eradication of approximately 40% to 80% (Simin 2007; Awad 2010). This indicates that there is an unmet need for drugs which can achieve a higher proportion of sustained virological response. With the new direct antiviral agents, higher proportions can be reached, but still not 100% (Bacon 2011; Jacobson 2011; Poordad 2011; Sherman 2011; Zeuzem 2011). Several studies have so far been published regarding the effects of aminoadamantanes. Our systematic review aims to assess

the benefits and harms of aminoadamantanes. This systematic review may have practical implications for the way patients with chronic hepatitis C are treated.

We are aware of a meta-analysis by Deltenre 2004, who studied the benefits and harms of aminoadamantanes for patients with chronic hepatitis C. A total of 31 randomised clinical trials including 4831 patients with chronic hepatitis C infection were included in this meta-analysis. Since 2004, new randomised clinical trials of aminoadamantanes have been conducted and our review therefore includes all the trials identified both before and after this meta-analysis.

Objectives

To assess the beneficial and harmful effects of aminoadamantanes for patients with chronic hepatitis C infection by conducting a systematic review with meta-analyses of randomised clinical trials, as well as trial sequential analyses.

Methods

Criteria for considering studies for this review

Types of studies

Randomised clinical trials assessing aminoadamantanes in patients with chronic hepatitis C infection irrespective of duration of treatment, language, publication type or status, and blinding. We excluded quasi-randomised studies or other observational studies captured during the search process from the reporting of benefit but they were included for the reporting of harm. However, we did not conduct specific searches for the latter studies.

Types of participants

We included patients with chronic hepatitis C. The diagnosis was based on the presence of serum hepatitis C RNA plus elevated transaminases for more than six months, or chronic hepatitis documented by liver biopsy. We also included patients diagnosed with 'non-A, non-B' chronic hepatitis as some trials may have been conducted before hepatitis C RNA analyses were widely available.

Based on the existence of and response to previous antiviral treatment, we classified the included patients as naive (not previously treated with antivirals), relapsers (patients with a transient serological viral response to previous treatment with antivirals), or non-responders (patients without a serological viral response to previous treatment with antivirals).

We excluded patients with chronic hepatitis C who had undergone liver transplantation.

Types of interventions

We aimed to perform the following comparisons.

- Aminoadamantanes versus placebo or no intervention.
- Aminoadamantanes plus standard antiviral therapy versus standard antiviral therapy alone.
- High-dose aminoadamantanes versus low-dose aminoadamantanes.
- Long-duration aminoadamantanes versus short-duration aminoadamantanes.

Co-interventions were allowed if administered equally to the intervention groups.

Types of outcome measures

Primary outcomes

1. All-cause mortality or liver-related morbidity as a composite outcome: number of patients who died or who developed, for example, cirrhosis (compensated or decompensated), ascites, hepatic encephalopathy, or hepatocellular carcinoma during treatment.
2. Adverse events (according to the Code of Federal Regulations and ICH guidelines (ICH-GCP)): number of patients with either serious adverse events or treatment discontinuation due to any adverse event. An adverse event is defined as "Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment" (ICH-GCP 1997).
3. Quality of life (as reported in the trials).

Secondary outcomes

1. Failure of serum (or plasma) sustained virological response: number of patients with detectable hepatitis C RNA at least six months after treatment.
2. Failure of end of treatment virological response: number of patients with detectable hepatitis C RNA at the end of treatment.

3. Failure of histological response: number of patients without improvement of histology (inflammation score (grading) or fibrosis score (staging) as defined by the individual trials).
4. Number of patients without normalisation of alanine aminotransferase (ALT) or aspartate transaminase (AST) serum levels or both (defined by the individual trials) at end of treatment and end of follow-up.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Hepato-Biliary Group Controlled Trials Register (1996 to December 2013) (Gluud 2014), the Cochrane Central Register of Controlled Trials (CENTRAL) 2013, Issue 11 of 12 (1995 to December 2013), MEDLINE (1946 to December 2013), EMBASE (1974 to December 2013), and Science Citation Index EXPANDED (1900 to December 2013) (Royle 2003). We also searched the WHO International Clinical Trials Registry Platform (www.who.int/ictrp), Google Scholar, and Eudrapharm. We have provided the search strategies in Appendix 1. We performed the latest search in December 2013. We will improve the searches for any later updates, if necessary.

Searching other resources

We searched for further trials by reading the reference lists of the identified publications. We checked the retrieved review articles and meta-analyses in order to find randomised clinical trials not identified by the electronic searches. We searched the journals *Hepatology* and *Journal of Hepatology* for abstracts from various gastrointestinal meetings. We wrote to the principal authors of the identified randomised clinical trials to request additional information.

Data collection and analysis

Selection of studies

Two authors (ML, MB) independently inspected each reference identified by the searches and applied the inclusion criteria. For possibly relevant publications, or in cases of disagreement, we obtained the full article and inspected this independently. In cases where ML and MB still disagreed, CG was consulted.

Data extraction and management

Two authors (ML, MB) extracted data independently. In case of disagreement between the two authors, a third author (CG) arbitrated. We discussed the data extraction, documented decisions and, where necessary, contacted the authors of trials for clarification. Trials were identified by the name of the first author and year in which the trial was published in full and ordered chronologically.

We extracted, checked, and recorded the following data:

- Characteristics of trials: date, location and setting; publication status; sponsor (specified, known, or unknown); duration of follow-up; bias domains; sample size calculation.
- Characteristics of participants: number of participants in each group; age; sex; ethnicity; weight or body mass index; viral load at the beginning of treatment; degree of fibrosis at the beginning of treatment.
- Characteristics of interventions: dose and duration of aminoadamantanes, and any co-interventions.
- Characteristics of outcome measures: whenever possible, we recorded the number of events listed under 'outcomes' in each group of the trial; we extracted information about harms from observational studies.

We incorporated cross-over trials in meta-analysis by using the end of first period strategy, which indicates that the analysis is based on only the first period of the included trial.

Assessment of risk of bias in included studies

Methodological quality is defined as confidence that the design and reporting of a randomised clinical trial will restrict bias in the comparison of the intervention (Moher 1998). According to empirical evidence, risk of bias in a trial can be assessed using 'Risk of bias' domains (Schultz 1995; Moher 1998; Kjaergard 2001; Wood 2008; Lundh 2012; Savović 2012; Savović 2012a). These are the following.

Allocation sequence generation

- Low risk of bias: sequence generation was achieved using computer random number generation or a random number table. Drawing lots, tossing a coin, shuffling cards, and throwing dice are adequate if performed by an independent research assistant not otherwise involved in the trial.
- Uncertain risk of bias: the method of sequence generation was not specified.

- High risk of bias: the sequence generation method was not random.

Allocation concealment

- Low risk of bias: the participant allocations could not have been foreseen in advance of, or during, enrolment. Allocation was controlled by a central and independent randomisation unit. The allocation sequence was unknown to the investigators (for example, if the allocation sequence was hidden in sequentially numbered, opaque, and sealed envelopes).
- Uncertain risk of bias: the method used to conceal the allocation was not described so that intervention allocations may have been foreseen in advance of, or during, enrolment.
- High risk of bias: the allocation sequence was likely to be known to the investigators who assigned the participants.

Blinding of participants and personnel

- Low risk of bias: it was described that both the participants and the personnel were blinded, and the method of blinding was described, so that knowledge of group assignment was adequately prevented during the trial.
- Uncertain risk of bias: it was not described if the trial was blinded, or the trial was described as blind but the method of blinding was not described, so that knowledge of group assignment was possible during the trial.
- High risk of bias: the trial was not blinded, so that the group assignment was known during the trial.

Blinded outcome assessment

- Low risk of bias: outcome assessment was done blinded for all relevant outcomes, and the method of blinding was described, so that knowledge of group assignment was adequately prevented.
- Unclear: it was not described if outcome assessment was blinded, or the outcome assessment was described as blind, but the method of blinding was not described, so that knowledge of group assignment was possible.
- High risk of bias: outcome assessment was not blinded, so that the group assignment was known for outcome assessors.

Incomplete outcome data

- Low risk of bias: missing data were unlikely to make treatment effects depart from plausible values. Sufficient methods, such as multiple imputation, have been employed to handle missing data.
- Uncertain risk of bias: there was insufficient information to assess whether missing data in combination with the method used to handle missing data were likely to induce bias on the results.
- High risk of bias: the results were likely to be biased due to missing data.

Selective outcome reporting

- Low risk of bias: all outcomes were predefined (for example, in a published protocol) and reported, or all clinically relevant and reasonably expected outcomes were reported, which included all primary and secondary outcome measures as stated under 'Types of outcome measures'.
- Uncertain risk of bias: it is unclear whether all predefined and clinically relevant and reasonably expected outcomes were reported, which included all primary and secondary outcome measures as stated under 'Types of outcome measures'.
- High risk of bias: one or more clinically relevant and reasonably expected outcomes, which included all primary and secondary outcome measures as stated under 'Types of outcome measures', were not reported, and data on these outcomes were likely to have been recorded.

Vested interest bias

- Low risk of bias: if the trial's source(s) of funding did not come from any parties that might have conflicting interests (e.g., an amantadine manufacturer), or if any academic, professional, financial, or other benefits to the person responsible for the trial were independent of the direction or statistical significance of the trial results.
- Uncertain: if the source of funding was not clear, or if it was unclear if the person responsible for the trial stands to benefit according to the direction or statistical significance of the trial results.
- High risk of bias: if the trial's source of funding had a conflict of interest, or if any academic, professional, financial, or other benefits to the person responsible for the trial were dependent of the direction or statistical significance of the trial results.

We assessed all trials for risk of bias. If we judged the risk of bias in a trial as 'uncertain' or 'high' for a domain, then we considered the trial to have 'high risk of bias'. If we judged a trial as low risk of bias in all seven domains, then we considered the trial as 'low risk of bias'. If we judged a trial as low risk of bias in at least the four domains random sequence generation, allocation concealment, blinding of participants and personnel, and blinding of outcome assessment, then we judged it to have 'lower risk of bias'. By using the term 'lower risk of bias', we wished to signal that we were well aware that such trials might indeed have risk of bias.

We handled reporting biases following the recommendations of The Cochrane Collaboration (Higgins 2011). We assessed funnel plot asymmetry (Higgins 2011), even though asymmetric funnel plots are not necessarily caused by publication bias and publication bias does not necessarily cause asymmetry in a funnel plot (Egger 1997).

Measures of treatment effect

The treatment effects in this meta-analysis are dichotomous or continuous. We expressed dichotomous data as risk ratio (RR) with 95% confidence intervals (CI). We derived the number needed to treat to benefit (NNTB) from the risk difference (RD) in case it was significant. For continuous data, we used the mean difference if the outcomes of the trials were measured in the same way. Where appropriate, we used the standardised mean difference to combine trials that measured the same outcome but using different methods.

Unit of analysis issues

As unit of analysis we used the reported outcomes per intervention group within the randomised clinical trials. In case no randomised clinical trials were identified, the results of the prospective cohort studies obtained with the search were to be presented in a narrative way in the 'Discussion' section of the review.

Dealing with missing data

We did the following to deal with missing data.

- We contacted the original investigators to request missing data.
- We performed sensitivity analyses to assess how sensitive our results were to reasonable changes in the assumptions that were made. We performed our analyses based on the intention-to-treat principle using imputation for the outcomes. We used the following scenarios (Hollis 1999).

- Carry forward analysis: if participants had missing outcome data, we used the last reported observed response ('carry forward') in the nominator, and included all randomised participants in the denominator.
- Extreme case analysis favouring the experimental intervention ('best-worst' case scenario): none of the drop-outs and participants lost from the experimental group but all of the drop-outs and participants lost from the control group experienced the outcome, including all randomised participants in the denominator.
- Extreme case analysis favouring the control ('worst-best' case scenario): all drop-outs and participants lost from the experimental group but none from the control group experienced the outcome, including all randomised participants in the denominator.

Assessment of heterogeneity

We assessed heterogeneity using the Chi^2 test of heterogeneity and quantified inconsistency with the I^2 statistic (Higgins 2002). In cases of substantial heterogeneity, as measured by a Chi^2 test with a P value less than 0.1 or an I^2 statistic value greater than 70%, we did not conduct meta-analysis. We assessed sources of clinical, methodological, and statistical heterogeneity in subgroup analyses.

Assessment of reporting biases

This is described under 'Assessment of risk of bias in included studies'.

Data synthesis

For the statistical analyses, we used Review Manager 5.2 (RevMan 2012). We meta-analysed the data with both a random-effects model (DerSimonian 1986) and a fixed-effect model (DeMets 1987) to ensure the robustness of the results. In case of differences in the results that the two models may have produced, we presented the results using both methods. If there were no differences in the results, we presented the results of the fixed-effect model only (Higgins 2011). If there was considerable variation in the results, and particularly if the direction of effect was inconsistent, it may be misleading to quote the average value for the intervention effect; we therefore interpreted the meta-analyses with utmost care.

Trial sequential analysis

Trial sequential analysis is a tool for quantifying the statistical reliability of data in cumulative meta-analysis, adjusting for sparse data, and repetitive testing of accumulating data (Brok 2008; Wetterslev 2008; Brok 2009a; Thorlund 2009, Wetterslev 2009; Thorlund 2010). Trial sequential analysis is a methodology that combines the calculation of a required information size (the sample sizes of the trials in the meta-analysis ought to answer a research question reliably) with the threshold of statistical significance (CTU 2011; Thorlund 2011).

Our intention was to perform trial sequential analysis primarily on the data from the trials with low risk of bias (Brok 2008; Wetterslev 2008). However, we chose to carry out trial sequential analysis on all trials because there were only a few trials with lower risk of bias. We analysed the outcome measures using trial sequential analysis no matter whether they yielded a statistically significant result in the meta-analysis or not. We used the meta-analytic estimate of the control event proportions of all trials, independent of risk of bias, as the control event proportion in the trial sequential analysis. We used the intervention effect estimated in the meta-analysis using all trials or used an a priori intervention effect of 20% risk ratio reduction. The unit of the intervention effect was risk ratio reduction for all dichotomous data.

For each trial sequential analysis performed, we calculated a diversity-adjusted required information size based on the intervention effect suggested by the trials with low risk of bias (LBHIS) or an a priori intervention effect of 20% risk ratio reduction, a risk of type I error of 5% and a risk of type II error of 20% or 10% (Wetterslev 2009). We performed the diversity adjustment using the observed diversity adjustment factor $(1/(1-D^2))$ where D^2 is the estimated heterogeneity among all trials and with an a priori assumed final diversity of 50% (Wetterslev 2009).

Subgroup analysis and investigation of heterogeneity

We planned the following subgroup analyses.

- Trials with low risk of bias compared to trials with high risk of bias.
- Type of patients, regarding previous antivirals, naives, relapsers, and non-responders as three separate groups, e.g., naives compared to relapsers.
- Type of patients, regarding genotype: genotype 1 compared to genotype non-1.
- Type of patients, regarding degree of liver disease (inflammation score (grading) or fibrosis score (staging)).

- Type of patients, regarding HIV or hepatitis B co-infection compared to patients without co-infection.
- Type of patients, regarding age: children compared to adults.
- Intervention: according to the type, dose, and duration of aminoadamantanes and other antiviral drugs.

We compared subgroups with a test of interaction (Altman 2003).

Sensitivity analysis

We identified suitable sensitivity analyses during the review process. For example, we used a sensitivity analysis when imputing missing data with replacement values.

Data analysis in the included trials was according to the intention-to-treat principle as well as 'as treated' (per protocol) analysis.

Summary of findings

We created a 'Summary of findings' table, presenting the results of our review outcomes (GRADEpro).

Results

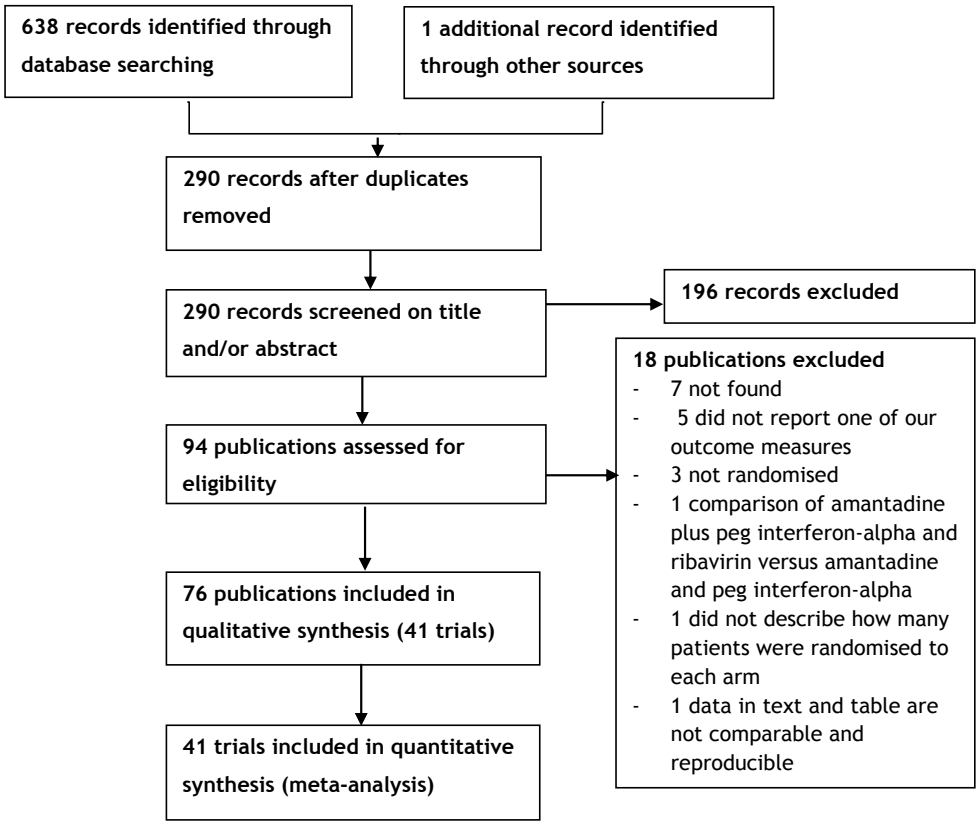
Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

Our search strategy identified 639 publications of potential interest. After filtering for duplicates 290 publications remained. Of the remaining 290 publications, we excluded 214 after screening the title and abstract, among other reasons because they were reviews or because they did not describe a randomised clinical trial investigating the effect of aminoadamantanes in patients with chronic hepatitis C. The remaining 76 references described 41 unique randomised clinical trials (Figure 1).

Figure 1. Flow diagram



Twenty-five of the included trials were published in more than one publication. Six out of 41 randomised clinical trials were published as abstracts only (Cornberg 2000; Shakil 2000; Jorge 2001; Vardar 2001; Teuber 2002; Calay 2005).

When necessary, we contacted the primary or last authors for further information and data relating to the trials. We searched for ongoing trials in the WHO International Clinical Trials Registry Platform (www.who.int/ictrp), Google Scholar, and Eudrapharm, but we did not identify any registered ongoing or planned trials.

Included studies

The included trials were 41 in total. Thirteen trials were conducted in Italy (Brillanti 1999; Brillanti 2000; Gaeta 2001; Mangia 2001; Tabone 2001; Bacosi 2002; Adinolfi 2003; Baisini 2003; Piai 2003; Angelico 2004; Ciancio 2006; Gramenzi 2007; Angelico 2008), seven trials

were conducted in Germany (Cornberg 2000; Zeuzem 2000; Teuber 2001; Teuber 2002; Berg 2003; Teuber 2003; von Wagner 2008), four trials were conducted in the USA (Shakil 2000; Smith 2004; Thuluvath 2004; Herrine 2005), three trials were conducted in Switzerland (Sax 2001; Helbling 2002; Wenger 2007), and two trials were conducted both in France and the UK (Caronia 2001; Caronia 2001a; Calay 2005; Maynard 2006). Other trials were conducted in each of the following different countries: Argentina, Austria, Belgium, Brazil, Kuwait, Mexico, The Netherlands, Spain, Taiwan, and Turkey (see Characteristics of included studies).

The first of the included trials was published in 1999 (Brillanti 1999) and the last in 2012 (Pessoa 2012). Thirty-six trials had a parallel-group design with two intervention groups. Two trials included three intervention groups (Bacosi 2002; Gramenzi 2007) and two trials included four intervention groups (Herrine 2005; Salmeron 2007). One trial had a cross-over group design (Smith 2004).

A total of 6193 patients with chronic hepatitis C were randomised to an amantadine arm or a control arm in the 41 clinical trials.

Only one trial compared amantadine monotherapy with placebo without additional antiviral drugs (Smith 2004). Seventeen trials compared amantadine plus interferon-alpha versus placebo or no intervention plus interferon-alpha (Characteristics of included studies). One out of these 17 trials also compared amantadine plus interferon-alpha and ribavirin versus placebo or no intervention plus interferon-alpha and ribavirin (Salmeron 2007). Eleven trials reported on the comparison of amantadine plus interferon-alpha plus ribavirin versus placebo or no intervention plus interferon-alpha plus ribavirin (Characteristics of included studies). Twelve trials compared amantadine plus peg interferon-alpha plus ribavirin versus placebo or no intervention plus peg interferon-alpha plus ribavirin (Characteristics of included studies).

The amantadine dose was the same in each trial: 200 mg daily, except for one trial, which prescribed 400 mg per day (von Wagner 2008). The treatment duration of the trials varied from 6 to 12 months. A six-month post-treatment duration of follow-up was used in all trials, except for four trials which applied 12 months of post-treatment follow-up (Bacosi 2002; Adinolfi 2003; Yang 2003; van Soest 2010) and one trial which applied 18 months of post-treatment follow-up (Ciancio 2006). The details are displayed in Table 1.

Table 1. Summary of characteristics of the included trials

Trial	Risk of bias	Trial duration (months)	Follow-up duration (months)
Amantadine versus placebo			
Smith 2004	Lower	6	6
Amantadine plus interferon versus placebo or no intervention plus interferon			
Angelico 2004	High	12	6
Bacosi 2002	High	12	12
Baisini 2003	High	12	6
Caronia 2001	High	12	6
Caronia 2001a	High	12	6
Gaeta 2001	High	6	6
Helbling 2002	High	12	6
Jorge 2001	High	12	6
Mangia 2001	High	12	6
Salmeron 2007	High	12	6
Sax 2001	High	12	6
Shakil 2000	High	6	6
Tabone 2001	High	12	6
Teuber 2001	High	12	6
Vardar 2001	High	6	6
Yang 2003	High	6	12
Zeuzem 2000	High	12	6
Amantadine plus interferon plus ribavirin versus placebo or no intervention plus interferon plus ribavirin			
Adinolfi 2003	High	12	12
Berg 2003	Lower	12	6
Brillanti 1999	High	6	6
Brillanti 2000	High	12	6
Cornberg 2000	High	12	6
Gramenzi 2007	High	12	6
Piai 2003	High	12	6
Salmeron 2007	High	12	6
Teuber 2002	High	12	6
Teuber 2003	High	12	6
Thuluvath 2004	High	12	6
Wenger 2007	High	12	6
Amantadine plus peg interferon plus ribavirin versus placebo or no intervention plus peg interferon plus ribavirin			
Angelico 2008	High	12	6
Calay 2005	High	12	6
Ciancio 2006	High	12	18
Ferenci 2006	High	12	6
Hasan 2004	High	12	6
Herrine 2005	High	12	6
Langlet 2009	High	6/12	6
Maynard 2006	High	12	6
Mendez-Navarro 2010	High	12	6
Pessoa 2012	High	12	6
van Soest 2010	High	12	12
von Wagner 2008	High	12	6

None of the trials compared one amantadine dose versus another. None of the trials compared head-to-head long-duration amantadine versus short-duration amantadine.

From the publications which reported the sex of the participants, more than 63% were males. All trials included adult patients, except for one trial which included children of one year or older (Smith 2004). Only one trial included HIV co-infected patients (Sax 2001). None of the trials included patients co-infected with hepatitis B.

Excluded studies

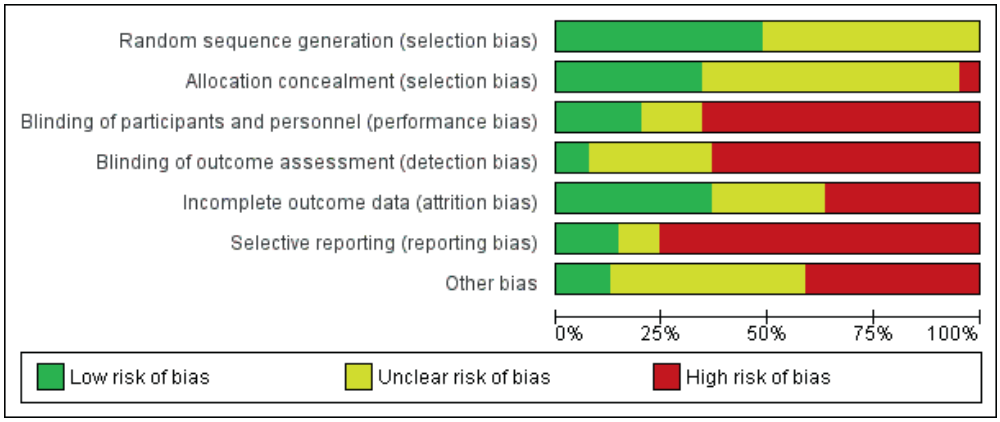
The excluded studies are listed under Characteristics of excluded studies and the reasons for exclusion are given there.

Risk of bias in included studies

We assessed risk of bias according to seven domains: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; handling of incomplete outcome data; selective outcome reporting; and vested interest bias. Other potential sources of bias for the individual trial, but not for the meta-analyses of such trials, were: baseline imbalance and early stopping.

We considered all included trials to have high risk of bias. We considered only two out of 41 trials as having lower risk of bias (Berg 2003; Smith 2004). Our statistical analyses are, therefore, based mainly on trials with high risk of bias. None of them had low risk of bias. For details of the judgements made for the individual trials, please see Figure 2 and Figure 3.

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



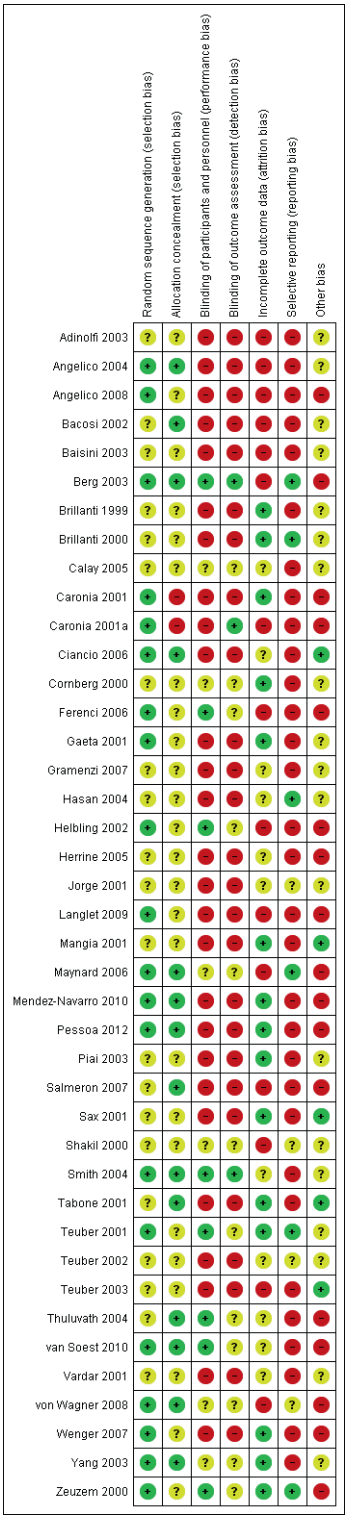


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

Allocation

The generation of the allocation sequence was adequately described in 20 trials (Characteristics of included studies). The remaining 21 trials were described as randomised but the method of random sequence generation was not described (Characteristics of included studies).

The method used to conceal allocation was adequately described in 14 trials (Characteristics of included studies). We judged the method for allocation concealment as unclear in 25 trials (Characteristics of included studies) and as high risk of bias in two trials (Caronia 2001; Caronia 2001a).

Blinding

The method of blinding of participants and personnel was adequately described in only eight trials (Zeuzem 2000; Teuber 2001; Helbling 2002; Berg 2003; Smith 2004; Thuluvath 2004; Ferenci 2006; van Soest 2010). We considered 33 trials as high risk of bias regarding blinding of participants and personnel (Characteristics of included studies). Three trials adequately described the method of blinding of outcome assessment (Caronia 2001a; Berg 2003; Smith 2004). Thus, the other 38 trials had high risk of bias (Characteristics of included studies). Only two trials had low risk of bias, with both blinding of participants and personnel and blinding of outcome assessments (Berg 2003; Smith 2004).

Incomplete outcome data

Incomplete data were addressed adequately in 15 trials (Brillanti 1999; Brillanti 2000; Cornberg 2000; Zeuzem 2000; Caronia 2001; Gaeta 2001; Mangia 2001; Sax 2001; Tabone 2001; Teuber 2001; Piai 2003; Yang 2003; Wenger 2007; Mendez-Navarro 2010; Pessoa 2012). In 26 trials there were risks of incomplete outcome data (Characteristics of included studies).

Selective reporting

Predefined, clinically relevant and reasonably expected primary and secondary outcomes were adequately assessed in only six clinical trials (Brillanti 2000; Zeuzem 2000; Teuber 2001; Berg 2003; Hasan 2004; Maynard 2006). Accordingly, there were risks of selective reporting of outcomes in 35 trials (Characteristics of included studies).

Other potential sources of bias

Five trials did not receive funding and were at low risk of bias regarding vested interests (Mangia 2001; Sax 2001; Tabone 2001; Teuber 2003; Ciancio 2006). Seventeen trials received funding from the medical industry. It was unclear whether trials received funding from the medical industry in 19 trials. We considered these last 36 trials as having high risk of bias because industrial sponsorship could introduce bias.

There were no baseline differences in any of the trials, except for two in which baseline imbalance was unknown (Sax 2001; Piai 2003). One trial stopped early due to poor results (Salmeron 2007).

Effects of interventions

See: Summary of findings for the main comparison

Amantadine versus placebo or no intervention

Primary outcomes

All-cause mortality or liver-related morbidity (composite outcome)

Thirty-two trials provided information on all-cause mortality or liver-related morbidity and could be included in the analyses. These 32 trials included one trial comparing amantadine versus placebo (Smith 2004), 14 trials comparing amantadine plus interferon-alpha versus

placebo or no intervention plus interferon-alpha, 10 trials comparing amantadine plus interferon-alpha and ribavirin versus placebo or no intervention plus interferon-alpha and ribavirin, and eight trials comparing amantadine plus peg interferon-alpha and ribavirin versus placebo or no intervention plus peg interferon-alpha and ribavirin. It should be noted that one trial included four treatment groups and was part of two treatment subgroups (Salmeron 2007) (Analysis 1.1). The included trials reported five deaths or liver-related morbidities in 2353 (0.2%) participants in the amantadine group versus six out of 2264 (0.3%) patients in the control group (Analysis 1.1). Meta-analyses with both the fixed-effect model and random-effects model showed no significant effect of amantadine, when compared with placebo or no intervention, on all-cause mortality or liver-related morbidity (fixed-effect model: risk ratio (RR) 0.90, 95% confidence interval (CI) 0.38 to 2.17; I^2 = 0%) (Analysis 1.1).

The subgroup analyses stratifying the trials according to risk of bias and according to previous treatment and treatment response with antivirals (for example, naive or non-responder patients) did not reveal any significant subgroup differences in effect estimates for the risk of all-cause mortality or liver-related morbidity (Analysis 2.1; Analysis 4.1).

Inspection of the funnel plot did not suggest bias (Figure 4).

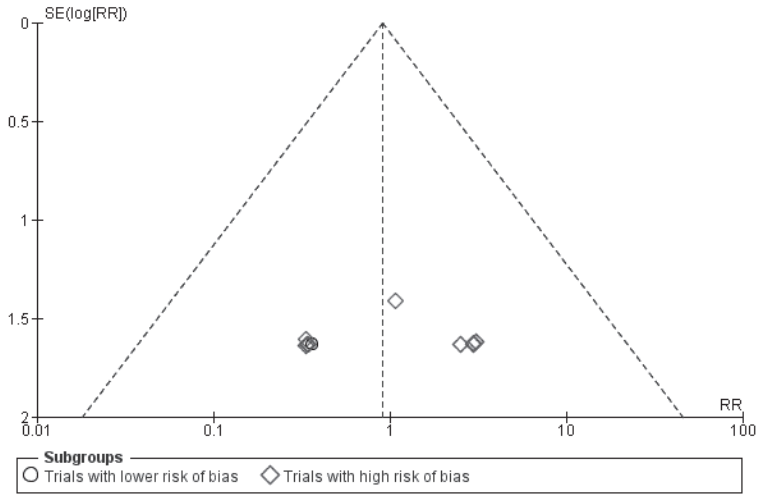


Figure 4. Funnel plot

Subgroup: trials at lower risk versus high risk of bias.

Outcome: 4.1 All-cause mortality or liver-related morbidity.

Fourteen trials provided information on all-cause mortality or liver-related morbidity in patients treated with amantadine plus interferon-alpha versus placebo or no intervention plus interferon-alpha. In the amantadine group, two out of 813 (0.2%) patients died or experienced a liver-related morbidity and in the control group two out of 758 (0.3%) patients died or had a liver-related morbidity. Meta-analysis showed no significant effect of amantadine plus

interferon-alpha when compared to placebo or no intervention plus interferon-alpha (fixed-effect model: RR 1.01, 95% CI 0.26 to 3.98; I^2 = 0%) (Analysis 1.1).

Zero deaths or liver-related morbidities were reported in 10 trials which conducted treatment with amantadine plus interferon-alpha and ribavirin compared with placebo or no intervention plus interferon-alpha and ribavirin (Analysis 1.1).

Eight trials reported on all-cause mortality or liver-related morbidity in patients treated with amantadine plus peg interferon-alpha and ribavirin versus placebo or no intervention plus peg interferon-alpha and ribavirin (Analysis 1.1). Three out of 933 (0.3%) patients treated with amantadine plus peg interferon-alpha and ribavirin, and three out of 897 (0.3%) patients treated with placebo or no intervention plus peg interferon-alpha and ribavirin, died or experienced liver-related morbidities. The risk ratio for this event was statistically non-significant when comparing amantadine plus peg interferon-alpha and ribavirin with placebo or no intervention plus peg interferon-alpha and ribavirin (fixed-effect model: RR 0.97, 95% CI 0.28 to 3.39; I^2 = 0%) (Analysis 1.1).

We considered only two trials as lower risk of bias, therefore we deemed it unnecessary to perform trial sequential analysis with these two trials only. Consequently, we performed trial sequential analysis on all included trials that reported on the composite outcome 'all-cause mortality or liver-related morbidity'. Due to lack of accurate reporting on all-cause mortality and liver-related morbidity in a number of trials, we were not able to gather enough information to support or refute the effect of amantadine on all-cause mortality or liver-related morbidity (see Figure 5).

Adverse events

We classified adverse events into two groups: number of patients with serious adverse events or number of patients with treatment discontinuation due to any adverse event.

Two-hundred and eighty-eight patients out of 2869 (10.0%) in the amantadine group with or without additional therapy versus 293 patients out of 2777 (10.6%) in the control placebo or no intervention group with or without additional therapy were reported to have either serious adverse events or treatment discontinuation due to any adverse event (Analysis 1.2).

The risk ratio for both events as a composite outcome was statistically non-significant when comparing amantadine with or without additional intervention versus placebo or no intervention with or without the same additional intervention (fixed-effect model: RR 0.98, 95% CI 0.84 to 1.14; I^2 = 0%; 5646 participants, 35 trials) (Analysis 1.2).

As there were no trials with low risk of bias, we performed trial sequential analysis on all included trials reporting on adverse events. Trial sequential analysis of these data supports the statistically non-significant finding (Figure 6).

Figure 5. Trial sequential analysis on all-cause mortality or liver-related morbidity
All cause mortality or liver related morbidity DARIS Pc 2%, RRR 20%, a 5%, b 20%, D 0% in a Two-sided graph.

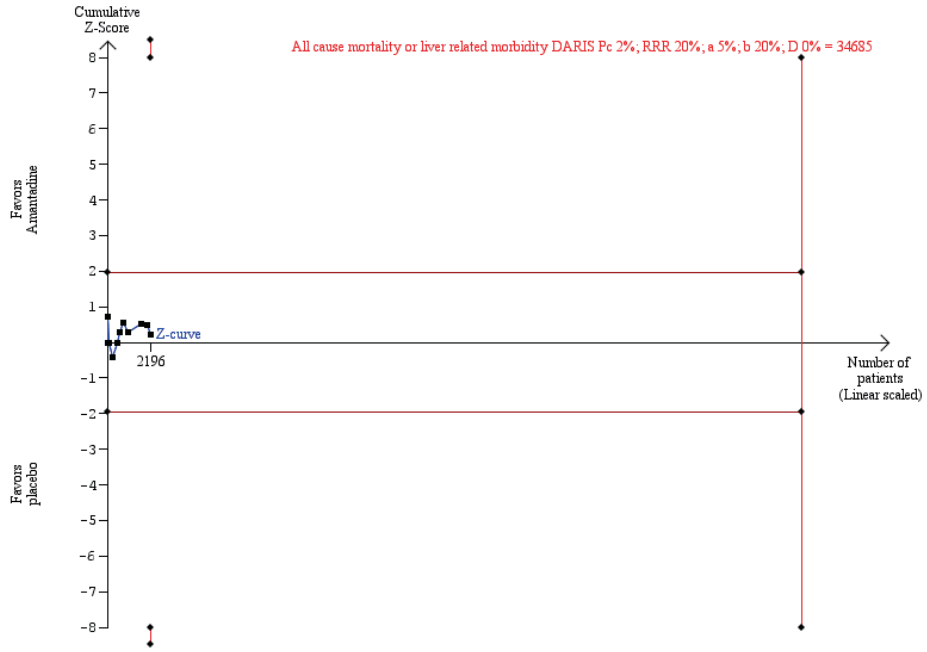


Figure 5: Trial sequential analysis of the random-effects meta-analysis of the effect of amantadine versus placebo or no intervention on all-cause mortality or liver-related morbidity in patients with chronic hepatitis C infection. The trial sequential analysis is performed with a type 1 error of 5% (two-sided), a power of 80%, an assumed control proportion of death or liver-related morbidity of 2%, and an anticipated relative risk reduction (RRR) of 20%. The diversity-adjusted required information size (DARIS) to detect or reject a RRR of 20%, with a between-trial heterogeneity of 0%, is estimated at 34,685 participants. The number of participants actually accrued is 2196, which is only 6% of the required information size. The blue cumulative Z-curve does not cross the red trial sequential monitoring boundaries for benefit or harm. Therefore, there is no evidence to support or refute the assumption that amantadine influences all-cause mortality or liver-related morbidity. The cumulative Z-curve does not reach the futility area (which is not even drawn by the program), demonstrating that further randomised trials may be needed.

Figure 6. Trial sequential analysis on serious adverse events or patients discontinuation treatment due to an adverse event

SAE or AE discontinuation DARIS Pc 11%, RRR 20%, a 5%, b 20%, D 0% in a Two-sided graph.

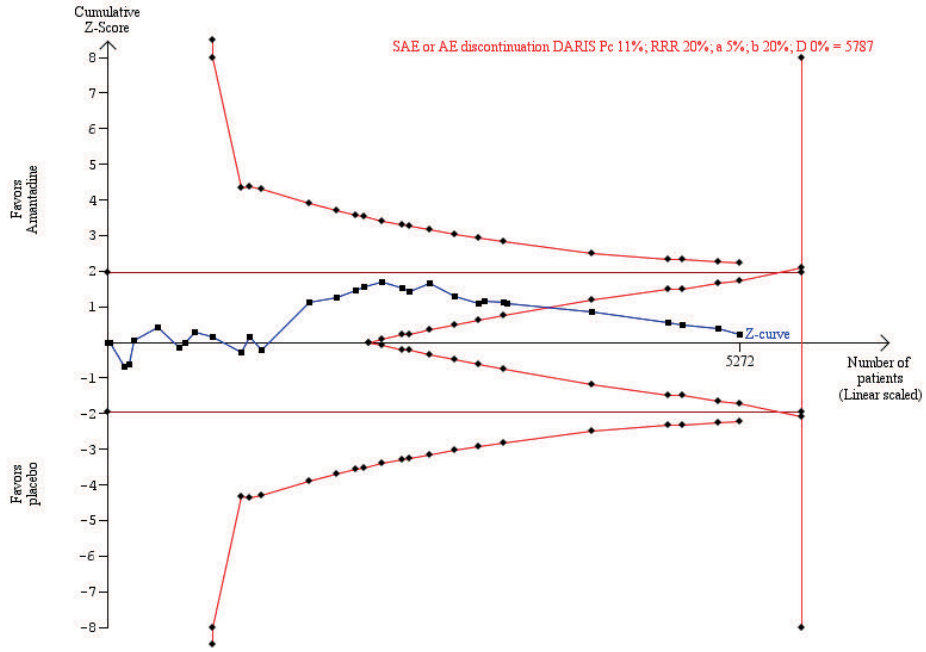


Figure 6: Trial sequential analysis of the random-effects meta-analysis of the effect of amantadine versus placebo or no intervention, in chronic hepatitis C-infected patients, on the number of patients experiencing a serious adverse event or the number of patients who had to discontinue treatment due to an adverse event. The trial sequential analysis is performed with a type 1 error of 5% (two-sided), a power of 80%, an assumed control proportion of number of patients experiencing a serious adverse event or who had to discontinue treatment due to an adverse event of 10%, and an anticipated relative risk reduction (RRR) of 20%. The diversity-adjusted required information size (DARIS) to detect or reject a RRR of 20%, with a between-trial heterogeneity of 0%, is estimated at 5787 participants. The number of participants actually accrued is 5272, which is 91% of the required information size. The blue cumulative Z-curve does not cross the red trial sequential monitoring boundaries for benefit or harm. Therefore, there is no evidence to support the assumption amantadine influences the number of patients experiencing a serious adverse event or who have to discontinue treatment due to an adverse event. The cumulative Z-curve does cross the trial sequential beta-spending monitoring boundaries and reach the futility area, demonstrating that no further randomised trials may be needed.

Inspection of the funnel plot did not suggest bias (Figure 7).

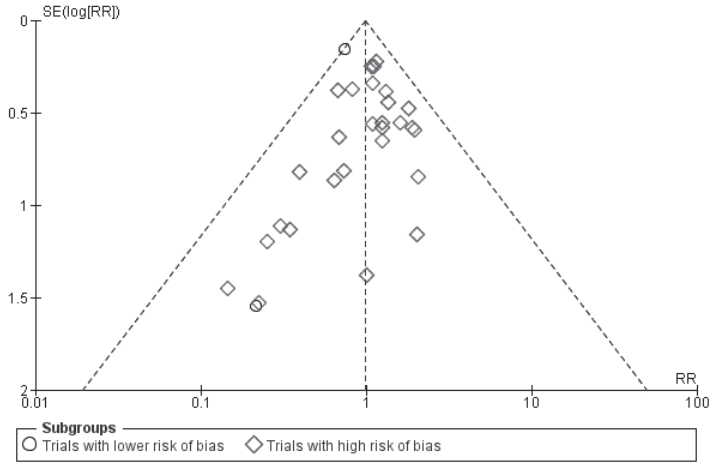


Figure 7. Funnel plot
Subgroup: trials at lower risk versus high risk of bias. Outcome: 4.2 Adverse events.

Quality of life

Only six trials reported on quality of life (Zeuzem 2000; Teuber 2001; Helbling 2002; Berg 2003; Smith 2004; Ferenci 2006). Three trials applied the 'Profile of Mood Status' scale (POMS) and the 'Everyday Life' questionnaire (EDLQ) (Zeuzem 2000; Teuber 2001; Berg 2003). The other three trials used a health-related quality of life (HRQoL) score (Ferenci 2006), VAS score (Helbling 2002), or the McMaster Quality of Life Survey (Smith 2004). We were not able to perform meta-analyses on quality of life due to a lack of valid data. Overall, we found no significant differences between treatment with amantadine when compared with placebo or no intervention in each separate trial.

Secondary outcomes

Failure of serum (or plasma) sustained virological response

Thirty-five trials provided information on patients who failed to achieve a sustained virological response. In the amantadine group, 1821 out of 2861 (63.6%) patients did not achieve a sustained virological response versus 1737 out of 2721 (63.8%) patients in the control group. Meta-analyses with both the fixed-effect model and random-effects model showed no significant effect of amantadine on failure to achieve a sustained virological response (fixed-effect model: RR 0.98, 95% CI 0.95 to 1.02; I^2 = 35%) (Analysis 1.4).

Thirteen trials reported on failure to achieve a sustained virological response in patients treated with amantadine plus interferon-alpha versus placebo or no intervention plus

interferon-alpha (Analysis 1.4). Five-hundred and sixty-four patients failed to achieve a sustained virological response out of 687 patients (82.1%) in the amantadine group versus 514 patients out of 626 patients (82.1%) in the control group. Meta-analysis showed no significant effect of amantadine plus interferon-alpha compared with placebo or no intervention plus interferon-alpha (fixed-effect model: RR 0.99, 95% CI 0.94 to 1.04; I^2 = 37%) (Analysis 1.4).

Eleven trials provided information on failure to achieve a sustained virological response in patients treated with amantadine plus interferon-alpha and ribavirin versus placebo or no intervention plus interferon-alpha and ribavirin (Analysis 1.4). Four-hundred and twenty-two patients failed to achieve a sustained virological response out of 666 (63.4%) patients in the amantadine group versus 447 out of 628 (71.2%) patients in the control group. Meta-analysis with both the fixed-effect model and random-effects model showed a significant effect of amantadine plus interferon-alpha and ribavirin when compared with placebo or no intervention plus interferon-alpha and ribavirin (fixed-effect model: RR 0.89, 95% CI 0.83 to 0.96; I^2 = 41%) (Analysis 1.4).

We analysed the missing data using a best-worst case scenario (assuming that participants receiving amantadine with an unknown status for achieving a sustained virological response did achieve this and that all participants from the control group with an unknown status for achieving a sustained virological response did not). This reveals a statistically significant effect favouring amantadine in patients treated with amantadine plus interferon-alpha and ribavirin (best-worst case scenario: RR 0.69, 95% CI 0.56 to 0.85; 1294 participants, 11 trials) (Analysis 5.1). We also analysed the missing data using a worst-best case scenario (assuming that participants receiving amantadine with an unknown status for achieving a sustained virological response did not achieve this and that all participants from the control group with an unknown status for achieving this did). This analysis shows no significant differences (worst-best case scenario: RR 1.02, 95% CI 0.81 to 1.29; 1294 participants, 11 trials) (Analysis 5.1).

In 12 trials, 2975 patients were treated with amantadine plus peg interferon-alpha and ribavirin versus placebo or no intervention plus peg interferon-alpha and ribavirin (Analysis 1.4). Eight-hundred and thirty-five out of 1508 patients (55.4%) treated in the amantadine group compared with 776 out of 1467 patients (52.9%) in the control group failed to achieve a sustained virological response. The risk ratio for this event was statistically non-significant when comparing amantadine plus peg interferon-alpha and ribavirin therapy with placebo or no intervention plus peg interferon-alpha and ribavirin (fixed-effect model: RR 1.04, 95% CI 0.97 to 1.10; I^2 = 3%) (Analysis 1.4).

The subgroup analyses, stratifying the trials according to risk of bias, revealed no statistically significant differences in the risk ratio for failure to achieve a sustained virological response, with both the fixed-effect model and the random-effects model, when comparing trials with lower risk of bias (RR 0.85, 95% CI 0.70 to 1.03; 400 participants; one trial) to trials with high risk of bias (fixed-effect model: RR 1.00, 95% CI 0.96 to 1.03; 5182 participants, 35 trials) (Analysis 4.3).

Meta-analysis with both a fixed-effect model and random-effects model resulted in no significant difference in the effect estimates for the risk of failure to achieve a sustained virological response in the subgroup analysis of trials including genotype 1 patients (RR 1.00, 95% CI 0.94 to 1.06, I^2 = 6%) compared to trials including non-genotype 1 patients (RR 0.98, 95% CI 0.82 to 1.18; I^2 = 0%) (Analysis 3.1).

Lastly, subgroup analyses, stratifying the trials according to previous antiviral therapy, showed no statistically significant differences with both the fixed-effect model and the random-effects model (Analysis 2.3). Subgroup analyses regarding degree of liver disease, HIV or hepatitis B co-infection, and age could not be performed due to lack of data.

Inspection of the funnel plot did indicate bias (Figure 8).

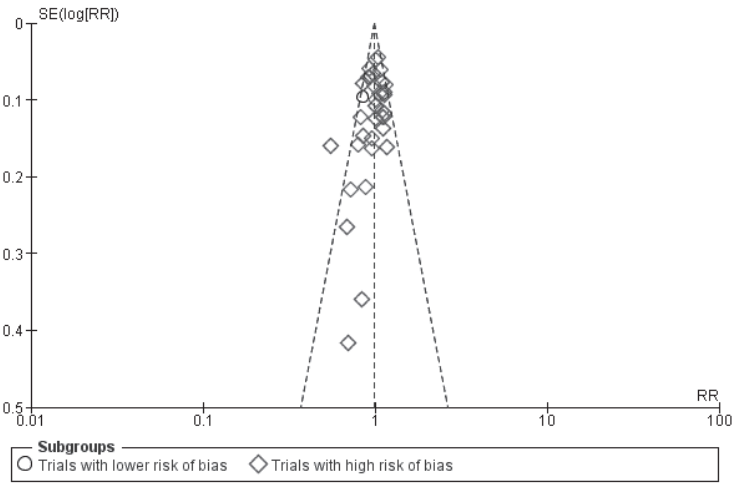


Figure 8. Funnel plot

Subgroup: trials at lower risk versus high risk of bias.
Outcome: 4.3 Failure of sustained virological response.

We performed trial sequential analysis on all trials, because we considered only two trials as lower risk of bias trials. Trial sequential analysis of the combined data supports the finding of no effect of amantadine, when compared with placebo or no intervention, on failure to achieve a sustained virological response (Figure 9). The result of the trial sequential analysis

is shown by the cumulated Z-curve (blue curve), which does not cross the trial sequential alpha spending monitoring boundary (red inward sloping curve) and ends up in the futility area. This implies that there is no evidence for a beneficial effect of amantadine in preventing failure to achieve a sustained virological response.

Figure 9. Trial sequential analysis on failure to achieve sustained virological response
Failure SVR DARIS Pc 64%, RRR 7%, a 5%, b 10%, D 35% in a Two-sided graph.

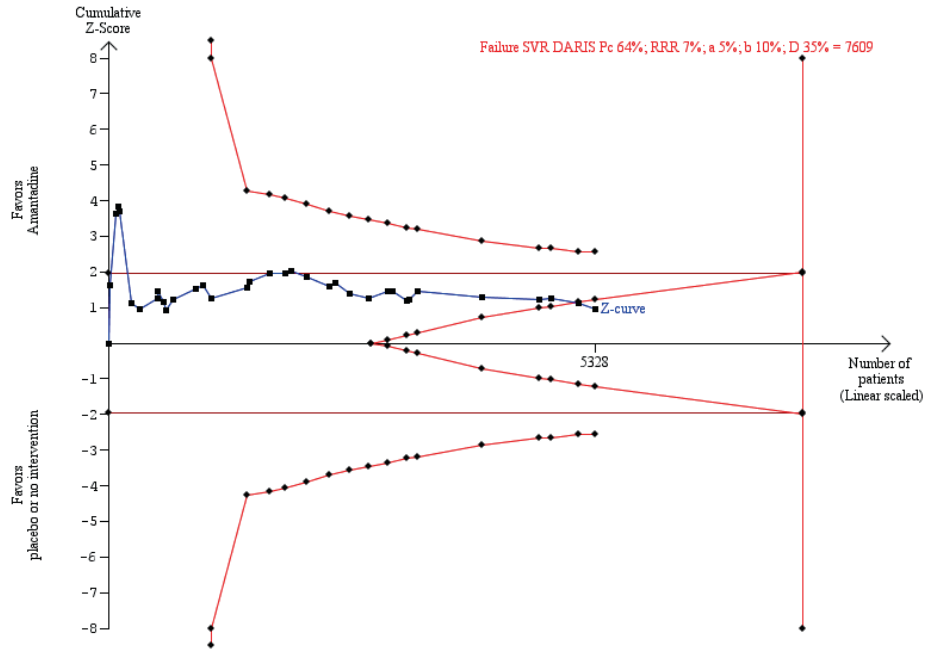


Figure 9: Trial sequential analysis of the random-effects meta-analysis of the effect of amantadine versus placebo or no intervention on the number of patients with chronic hepatitis C virus infection who failed to achieve a sustained virological response (SVR). The trial sequential analysis is performed with a type 1 error of 5% (two-sided), a power of 90%, an assumed control proportion of number of patients who failed to achieve a SVR of 64%, and an anticipated relative risk reduction (RRR) of 7%. The diversity-adjusted required information size (DARIS) to detect or reject a RRR of 7%, with a between-trial heterogeneity of 35%, is estimated at 7609 participants. The number of participants actually accrued is 5328, which is 70% of the required information size. The blue cumulative Z-curve does not cross the red trial sequential monitoring boundaries for benefit or harm. Therefore, there is no evidence to support the assumption that amantadine influences the number of patients who fail to achieve a SVR and it is likely that a 7% RRR in the number of patients who fail to achieve a SVR can be rejected with the chosen error risks. The cumulative Z-curve does reach the futility area, demonstrating that no further randomised trials may be needed.

We also performed trial sequential analysis on a subgroup, comparing failure to achieve a sustained virological response in patients treated with amantadine plus interferon-alpha and ribavirin with patients treated with interferon-alpha and ribavirin (Figure 10). There is no evidence to support or refute the assumption that amantadine influences the number of patients who fail to achieve a sustained virological response.

Figure 10. Trial sequential analysis on failure to achieve sustained virological response in subgroup treated with amantadine plus interferon-alpha and ribavirin versus placebo or no intervention plus interferon-alpha and ribavirin

Failure SVR subgroup AMA + IFN + RIBA vs IFN + RIBA DARIS Pc 71%, RRR 7%, a 5%, b 10%, D 12% in a Two-sided graph.

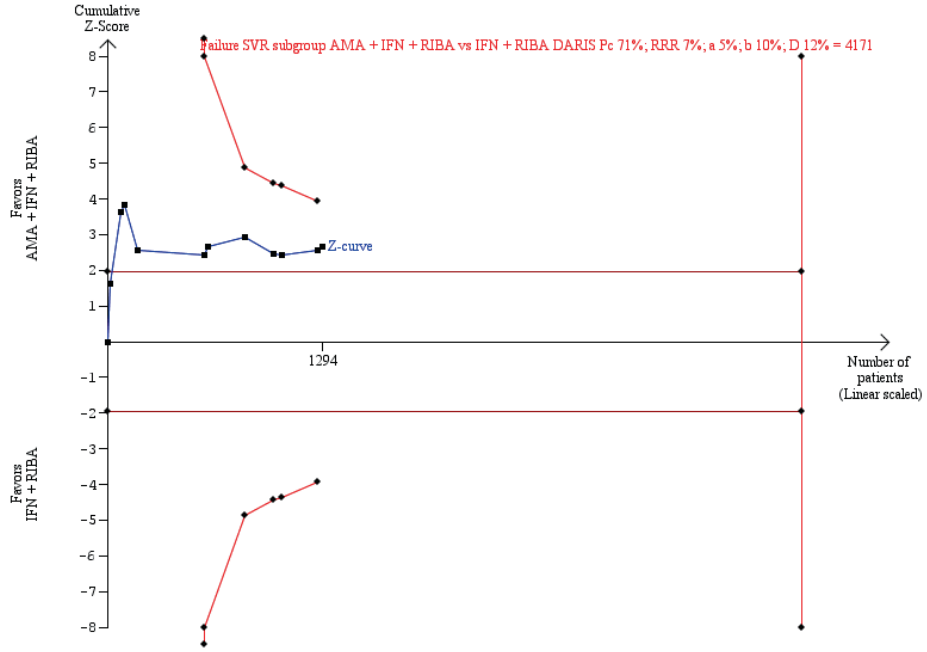


Figure 10: Trial sequential analysis of the random-effects subgroup meta-analysis of the effect of amantadine plus interferon-alpha and ribavirin versus placebo or no intervention plus interferon-alpha and ribavirin on the number of patients with chronic hepatitis C virus infection who failed to achieve a sustained virological response (SVR). The trial sequential analysis is performed with a type 1 error of 5% (two-sided), a power of 90%, an assumed control proportion of number of patients who failed to achieve a SVR response of 71%, and an anticipated relative risk reduction (RRR) of 7%. The diversity-adjusted required information size (DARIS) to detect or reject a RRR of 7%, with a between-trial heterogeneity of 12%, is estimated at 4171 participants. The number of participants actually accrued is 1294, which is only 31% of the required information size. The blue cumulative Z-curve does not

cross the red inward sloping trial sequential alpha-spending monitoring boundaries for benefit or harm. Therefore, there is no evidence to support the assumption that amantadine influences number of patients who fail to achieve a SVR and it is likely that a 7% RRR in the number of patients who fail to achieve a SVR on treatment with amantadine plus interferon-alpha and ribavirin can be rejected with the chosen error risks. The cumulative Z-curve does not reach the futility area (which is not even drawn by the program), demonstrating that further randomised trials may be needed.

Failure of end of treatment virological response

Thirty trials provided information on patients who failed to achieve an end of treatment virological response and could be included in the analyses (Analysis 1.3). In the amantadine group, 1288 out of 2483 patients (51.9%) did not achieve an end of treatment virological response versus 1268 out of 2378 patients (53.3%) in the control group. Meta-analyses with both the fixed-effect model and the random-effects model showed no significant effect of amantadine on achieving an end of treatment virological response (fixed-effect model: RR 0.95, 95% CI 0.90 to 1.00; I^2 = 43%) (Analysis 1.3).

Ten trials provided information on failure to achieve an end of treatment virological response in patients treated with amantadine plus interferon-alpha and ribavirin versus placebo or no intervention plus interferon-alpha and ribavirin (Analysis 1.3). Three-hundred and forty-nine patients failed to achieve an end of treatment virological response out of 625 patients (39.8%) in the amantadine group versus 386 out of 594 patients (65.0%) in the control group. Meta-analysis with both the fixed-effect model and the random-effects model showed a significant effect of amantadine plus interferon-alpha and ribavirin compared with placebo or no intervention plus interferon-alpha and ribavirin (fixed-effect model: RR 0.86, 95% CI 0.79 to 0.94; I^2 = 66%) (Analysis 1.3).

We analysed the data in a best-worst case scenario regarding missing data (assuming that participants with an unknown status for achieving an end of treatment virological response receiving amantadine did achieve this and that all participants from the control group with an unknown status for achieving an end of treatment virological response did not). This reveals a stronger positive statistical effect estimate favouring amantadine in patients treated with amantadine plus interferon-alpha and ribavirin (RR 0.58, 95% CI 0.52 to 0.65; 1219 participants, 10 trials) (Analysis 5.2). We also analysed the data in a worst-best case scenario regarding missing data (assuming that participants with an unknown status for an achieving end of treatment virological response receiving amantadine did not achieve this and that all participants from the control group with an unknown status for achieving an end of treatment

virological response did). This reveals an effect favouring the control (worst-best case scenario: RR 1.20, 95% CI 1.08 to 1.34; 1219 participants, 10 trials) (Analysis 5.2).

Failure of histological response

Only three trials provided information on the number of patients without improvement of histology (Shakil 2000; Zeuzem 2000; Baisini 2003) (Analysis 1.5). They included 24, 93, and 119 patients. Only 74 out of these 219 patients underwent a liver biopsy before treatment and after treatment. We cannot meta-analyse or draw any conclusions from these data.

Number of patients without normalisation of serum ALT and/or AST levels at end of treatment and at end of follow-up

All trials that reported on biochemical response reported ALT levels only. Therefore, we have chosen only to provide ALT levels in this analysis.

Nineteen trials provided information on failure to achieve end of treatment biochemical response. In the amantadine group, 671 out of 1141 (58.8%) patients did not achieve end of treatment biochemical response versus 732 out of 1100 (66.5%) patients in the control group. Meta-analyses with both the fixed-effect model and random-effects model showed that amantadine significantly decreases the number of patients without normalisation of ALT serum levels at the end of treatment compared with placebo or no intervention (fixed-effect model: RR 0.88, 95% CI 0.83 to 0.94; I^2 = 47%) (Analysis 1.6).

In seven trials, 207 out of 418 (49.5%) patients treated with amantadine plus interferon-alpha and ribavirin compared with 247 out of 390 (63.3%) patients in the control group treated with placebo or no intervention plus interferon-alpha and ribavirin failed to achieve an end of treatment biochemical response (Analysis 1.6). Meta-analysis with both the fixed-effect model and the random-effects model showed a significant effect of amantadine plus interferon-alpha and ribavirin compared with placebo or no intervention plus interferon-alpha and ribavirin (fixed-effect model: RR 0.79, 95% CI 0.70 to 0.89; I^2 = 70%) (Analysis 1.6).

Furthermore, 21 trials provided information on patients who failed to achieve an end of follow-up biochemical response and could be included in the analyses (Analysis 1.7). In the amantadine group, 1133 out of 1896 (59.8%) patients did not achieve an end of follow-up biochemical response versus 1151 out of 1848 (62.3%) patients in the control group. Meta-analyses with both models showed no significant effect of amantadine on achieving an end of

follow-up biochemical response (fixed-effect model: RR 0.95, 95% CI 0.91 to 1.00; I^2 = 49%) (Analysis 1.7).

Summary of findings

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) 'Summary of findings' table (Guyatt 2008) is shown in Summary of findings for the main comparison. We considered all outcomes for the 'Summary of findings' table except failure of histological response, due to lack of data.

Discussion

Summary of main results

We included 41 trials with a total of 6193 patients, which assessed the benefit and harm of amantadine when compared with placebo or no intervention in the treatment of patients with chronic hepatitis C. The effect of amantadine was evaluated in four different treatment strategies: monotherapy with amantadine, combination therapy of amantadine with interferon-alpha, combination therapy of amantadine plus interferon-alpha and ribavirin, and combination therapy of amantadine plus peg interferon-alpha and ribavirin. We carried out subgroup analyses according to a classification based on whether a patient had already received treatment for hepatitis C before and if so which treatment he/she had received, e.g., naive patients, relapsers, or non-responders. The present systematic review did not demonstrate any benefit of amantadine on all-cause mortality or liver-related morbidity for any of these treatment regimens or types of patients.

Our systematic review also showed that concomitant use of amantadine in the treatment of chronic hepatitis C is not associated with either an increase or a reduction in adverse events, defined as the number of patients who experienced a serious adverse event or had to discontinue treatment due to an adverse event. We confirmed these results by applying trial sequential analysis.

Moreover, amantadine did not decrease the overall proportion of patients who failed to achieve a sustained virological response. This finding was confirmed by a trial sequential analysis. However, in subgroup analysis we demonstrated that patients treated with a

combination therapy of amantadine plus interferon-alpha and ribavirin had statistically significant less failure in achieving a sustained virological response. However, trial sequential analysis could not exclude risks of random errors (play of chance) and all trials had risks of systematic errors (bias). When applying further subgroup analysis with both the fixed-effect model and the random-effects model, stratifying trials according to previous antiviral therapy or genotype, there were no significant differences in the effect estimates for the risk of failure to achieve a sustained virological response.

Unfortunately, we were not able to identify any convincing benefits of amantadine when assessing histology, because only three trials reported failure of histological improvement. For quality of life, we also could not identify any convincing benefits because only six trials reported this outcome. We found a significant benefit of adding amantadine to interferon-alpha-based therapy for biochemical response at the end of treatment, but not for end of follow-up response.

Overall completeness and applicability of evidence

This systematic review examined the evidence from 41 randomised clinical trials on the treatment of hepatitis C. Despite efforts to obtain additional information from the authors we could not obtain all relevant data, hence not all trials reported on all of our predefined outcomes.

Thirty-two trials reported adequately on our primary outcomes of all-cause mortality or liver-related morbidity, and 35 trials reported on serious adverse events and treatment discontinuation due to an adverse event. Only six trials provided information on quality of life. Thirty-six trials reported on our first secondary outcome measure: failure to achieve a sustained virological response. Twenty-nine trials reported on failure of end of treatment virological response. Only two trials provided information on failure of histological improvement, another 17 trials reported on failure of biochemical response at the end of treatment, and 19 trials reported on failure of biochemical response at the end of follow-up.

It is questionable whether the included patients are representative of current practice. All trials included patients with positive serum hepatitis C RNA. However, there was heterogeneity among the trials due to the different disease severity of the patients at trial entry, differences in genotype (35 trials included a mixture of genotypes), and differences regarding previous antiviral treatment. Concerning sex and age, the trials seem representative of current clinical care: more than 63% of the included patients were male and all included adult patients, except for one trial which included children of one year or older (Smith 2004).

However, only one trial included HIV co-infected patients (Sax 2001). None of the trials included patients co-infected with hepatitis B. There are therefore insufficient data on co-infected patients.

Quality of the evidence

We conducted this review according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and the Cochrane Hepato-Biliary Group Module (Gluud 2014). The results of our meta-analysis, however, are only as strong as the primary trials included.

The main limitation in the design and implementation of trials was the lack of clarity about the generation of the allocation sequence, concealment of allocation, and blinding. Of the 41 included trials, only 20 (49%) reported adequate allocation sequence generation, only 14 (35%) adequately reported allocation concealment, and only two (5%) reported blinding. Fifteen trials (37%) adequately addressed incomplete data, but only six trials (15%) reported all clinically relevant and reasonably expected outcomes. Also, only five trials (12%) appeared to be free of other components that could put them at risk of bias. Accordingly, 95% of trials were at high risk of bias. It is surprising to see that so many trials had high risk of bias, despite the repeated calls for improved trial quality both within and outside hepatology (Schultz 1995; Gluud 1998; Kjaergard 1999; Needleman 1999; Kjaergard 2001; Wood 2008; Savović 2012; Savović 2012a).

Regarding the precision of our results, some outcomes in our meta-analysis include few patients and few events, and thus have wide confidence intervals around the estimate of effect.

Potential biases in the review process

In this systematic review we performed a comprehensive literature search. As far as we know, we have found all the evidence available. A potential limitation of our literature search may be that we have not specifically searched for trials in the grey literature, which may have introduced a slight risk of bias into our meta-analysis (Egger 2003). However, this bias is unlikely to influence our results in a beneficial way as trials found in the grey literature rarely report beneficial effects.

Most of the included trials are of a relatively small size, especially those performed in the early 2000s. This increases the risk of an unrealistic estimate of the intervention effects due to bias (systematic errors) or chance (random errors). Risk of bias is known to have an impact

on the estimated intervention effect, with trials at high risk of bias overestimating beneficial intervention effects and underestimating harmful effects (Schultz 1995; Moher 1998; Kjaergard 2001; Wood 2008; Lundh 2012; Savović 2012; Savović 2012a). We divided the analysis for all outcomes into trials with high risk of bias and trials with lower risk of bias trials to reveal any influence of bias on the effect estimates of our outcomes. Of the 41 included trials, only two had lower risk of bias. We did not observe an influence of bias on any of our analyses, but due to there being few trials with lower risk of bias these analyses do not have sufficient power. The estimated intervention effects for all significant beneficial findings may therefore possibly be due to systematic errors.

No statistical signs of publication bias or other bias were observed.

This review pooled data for all-cause mortality or liver-related morbidity from 32 trials involving 4617 patients. We also pooled data for serious adverse events or treatment discontinuation due to an adverse event from 35 trials involving 5646 patients. The median trial duration was 12 months, with a median follow-up of six months (four trials had a follow-up of 12 months, one trial had a follow-up of 18 months). For our primary outcome measure, all-cause mortality or liver-related morbidity, this is not sufficiently long, considering that the estimated median time in which hepatitis C progresses to cirrhosis is 15 years to 50 years (Koretz 1993; Kenny-Walsh 1999; Seeff 2009). Therefore, it is difficult to detect a significant difference in all-cause mortality and liver-related morbidity based on these trials. If aminoadamantanes have an effect on morbidity and mortality one prerequisite would be that they significantly affect virological load. However, we were unable to provide viral data to demonstrate that this was the case.

We used trial sequential analysis to cope with the risk of random error, which is higher when information sizes are small (Wetterslev 2008). Trial sequential analysis of the primary outcomes, all-cause mortality or liver-related morbidity and serious adverse events or treatment discontinuation due to an adverse event, and of the secondary outcome measure, sustained virological response, showed no significant effect estimates when we applied both the random-effects and fixed-effect models in patients treated with amantadine.

Heterogeneity among the trials might be due to differences in dose, duration, and type of interferon-alpha or peg interferon-alpha. Both evaluation of this and long-term follow-up studies could be useful. Also different definitions of non-responders were used in the trials, such as non-responder to previous interferon-alpha therapy alone or non-responder to combination therapy of interferon-alpha with ribavirin. Furthermore, there could be

heterogeneity among trials due to the disease severity of patients at entry and differences in genotype, which can both affect the sustained virological response rates. To reflect our concern about heterogeneity, we conducted all analyses using both the fixed-effect model and the random-effects model. We only presented the results of the fixed-effect model if the results of the two models did not differ. We also considered other important and predefined trial-level covariates, including trial risk of bias, genotype distribution, and previous antiviral treatment. Subgroup analyses of other predefined covariates, such as degree of liver disease, could not be performed because of the lack of trials reporting on this outcome.

Lastly, we did not analyse the two amantadine modalities, amantadine hydrochloride and amantadine sulphate.

Agreements and disagreements with other studies or reviews

It is likely that less than 10% of all infected patients will develop end-stage liver disease. Overall, we found that amantadine did not show any benefit for all-cause mortality or liver-related morbidity. Most trials reported on the surrogate outcome measure sustained virological response, but as already mentioned, we do not know whether a sustained virological response results in less mortality or morbidity (Gluud 2007). An observation was that, while those treated with interferon-alpha and ribavirin were allegedly more likely to develop a sustained virological response if amantadine was added, there was no difference in all-cause mortality or liver-related morbidity (although this observation is certainly limited by the short follow-up periods). This is in accordance with a number of findings in patients with chronic hepatitis C showing that a sustained virological response may not be a valid surrogate marker of clinical outcomes for a number of antiviral drugs (Brok 2010; Koretz 2013; Gurusamy 2013; Hauser 2014; Hauser 2014a).

Considering failure to achieve a sustained virological response, we also found that amantadine did not show any benefit, except for in the subgroup patients treated with the combination therapy of amantadine plus interferon-alpha and ribavirin, in which amantadine seems to complement the lack of efficacy of interferon-alpha compared with peg interferon-alpha. However, this finding was not supported by the trial sequential analyses. This result is in accordance with the main findings of a recently published meta-analysis (Chen 2012), which suggests that there is no beneficial effect of adding amantadine to peg interferon-alpha plus ribavirin in naive hepatitis C genotype 1 patients. Our findings are contrary to the main findings of another meta-analyses (Deltenre 2004), which suggested a role for amantadine in non-responder patients. Furthermore, our results are also in contrast with another review,

which suggests that there may be a limited role of combination therapy in naive patients (Lim 2005).

We have no evidence from randomised clinical trials on the long-term effects (more than one year) of amantadine on our primary outcomes. Long-term effects would be relevant in particular for outcomes such as all-cause mortality or liver-related morbidity.

Amantadine was generally well tolerated. We observed that amantadine was associated with non-serious adverse events and almost all trials in general reported similar frequencies and severities of adverse events in both amantadine groups versus control groups. This result is in accordance with a recently published Cochrane review of amantadine and rimantadine for influenza A in children and the elderly (Alves Galvão 2012). The result is also somewhat comparable to two other Cochrane reviews. The review of amantadine and rimantadine in influenza A in adults showed significantly more adverse effects in patients receiving amantadine compared with placebo, but no increased risk of serious adverse events (Jefferson 2012). The second review reported on amantadine in Parkinson's disease and found that there is not enough evidence from trials about the effects of amantadine for people with Parkinson's disease, but that adverse events in trials so far have not been severe (Crosby 2009). In our analysis, amantadine was administered with interferon-alpha or peg interferon-alpha with or without ribavirin, except for in one trial. Interferon-alpha-based therapy is typically associated with haematologic complications (i.e., neutropenia, thrombocytopenia), neuropsychiatric complications (i.e., memory and concentration loss, visual disturbances, headaches, depression, irritability), flu-like symptoms, hormonal complications (i.e., hypothyroidism, hyperthyroidism), gastrointestinal complications (i.e., nausea, vomiting, weight loss), and dermatologic complications (i.e., eczema, alopecia). The most well-known adverse effect of ribavirin is dose-dependent haemolytic anaemia but gastrointestinal adverse effects such as nausea are also reported (Chutaputti 2000; Soza 2002; Sulkowski 2004). In conclusion, both interferon-alpha and ribavirin are associated with a variety of adverse events of different severities, which may make it hard to detect less severe adverse events associated with amantadine. We cannot exclude the possibility of less severe adverse events with amantadine, for example gastrointestinal symptoms and insomnia.

Regarding tolerance of amantadine we have to take dosage into consideration. Only one trial used an amantadine dose of more than 200 mg per day (von Wagner 2008). One randomised clinical trial evaluated the safety and toxicity of amantadine in patients with chronic hepatitis C; it also investigated the maximum tolerable dose of amantadine (Smith 2004a). They reported an increase in biochemical response with higher daily doses of amantadine from 200

mg per day up to 500 mg per day in monotherapy. However, no statistically significant difference was found in alanine aminotransferase (ALT) values between those receiving 300 mg and those receiving higher doses of amantadine. Also, increasing the amantadine dose did not result in more patients achieving a sustained virological response, when comparing 200 mg per day with 300 mg to 500 mg per day (Smith 2004a).

Authors' conclusions

Implications for practice

This review shows that there seems to be no significant beneficial effect of amantadine on all-cause mortality or liver-related morbidity composite outcome, or on adverse events in hepatitis C-infected patients; although the timeframe for measuring the composite outcome was insufficient in the included randomised clinical trials. Furthermore, amantadine did not increase the proportion of patients with a sustained virological response. In the absence of convincing evidence of benefit, the use of amantadine is justified in the context of randomised clinical trials assessing the effects of combination therapy with peg interferon-alpha and ribavirin. We found no randomised clinical trials assessing other aminoadamantanes.

Implications for research

Given the results of our analysis, we cannot conclude whether new randomised clinical trials will or will not find any beneficial effect of amantadine on patients' survival in chronic hepatitis C patients. In subgroup analyses we observed that therapy with amantadine plus interferon-alpha and ribavirin compared with interferon-alpha and ribavirin seems to increase the number of patients with a sustained virological response, but this effect was not supported by our trial sequential analysis. We did not observe a similar finding when examining amantadine combined with peg interferon-alpha and ribavirin. Therefore, to prove the former effect, further randomised clinical trials would be required. We found no evidence for other aminoadamantanes. Based on the overall evidence, future trials assessing amantadine, or potentially other aminoadamantanes for patients with chronic hepatitis C, may not show strong benefits. Therefore, it is probably advisable to wait for the results of trials assessing other direct-acting antiviral drugs. Amantadine and other aminoadamantanes should only be used within randomised clinical trials; they do not appear to have a place in usual clinical practice. To our knowledge, no ongoing trials are investigating the effects of amantadine in

hepatitis C patients. Any further trials should be designed according to the SPIRIT guidelines (SPIRIT 2013; SPIRIT 2013a), and conducted and reported according to the CONSORT Statement (Schulz 2012).

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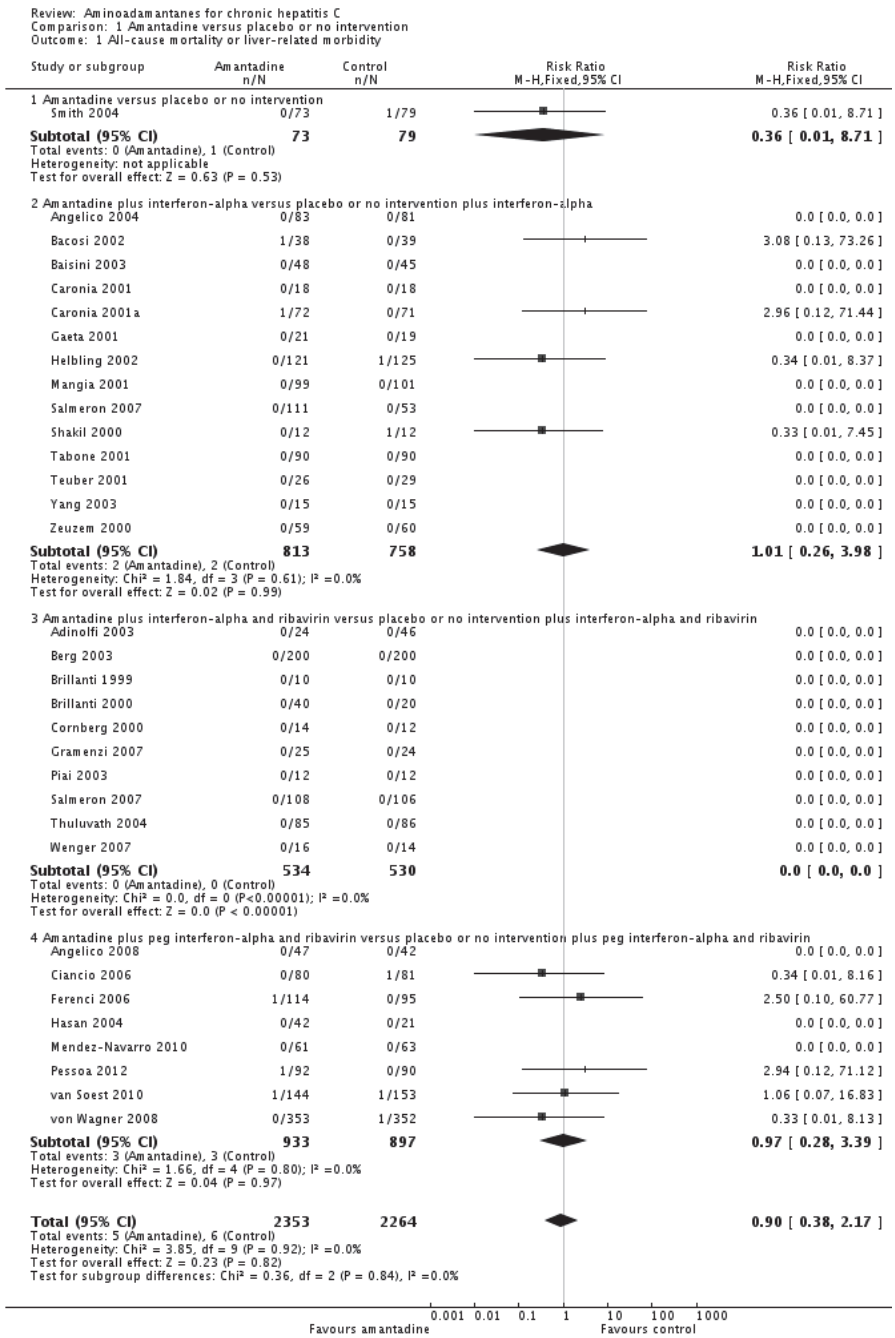
Data and analyses

Comparison 1. Amantadine versus placebo or no intervention

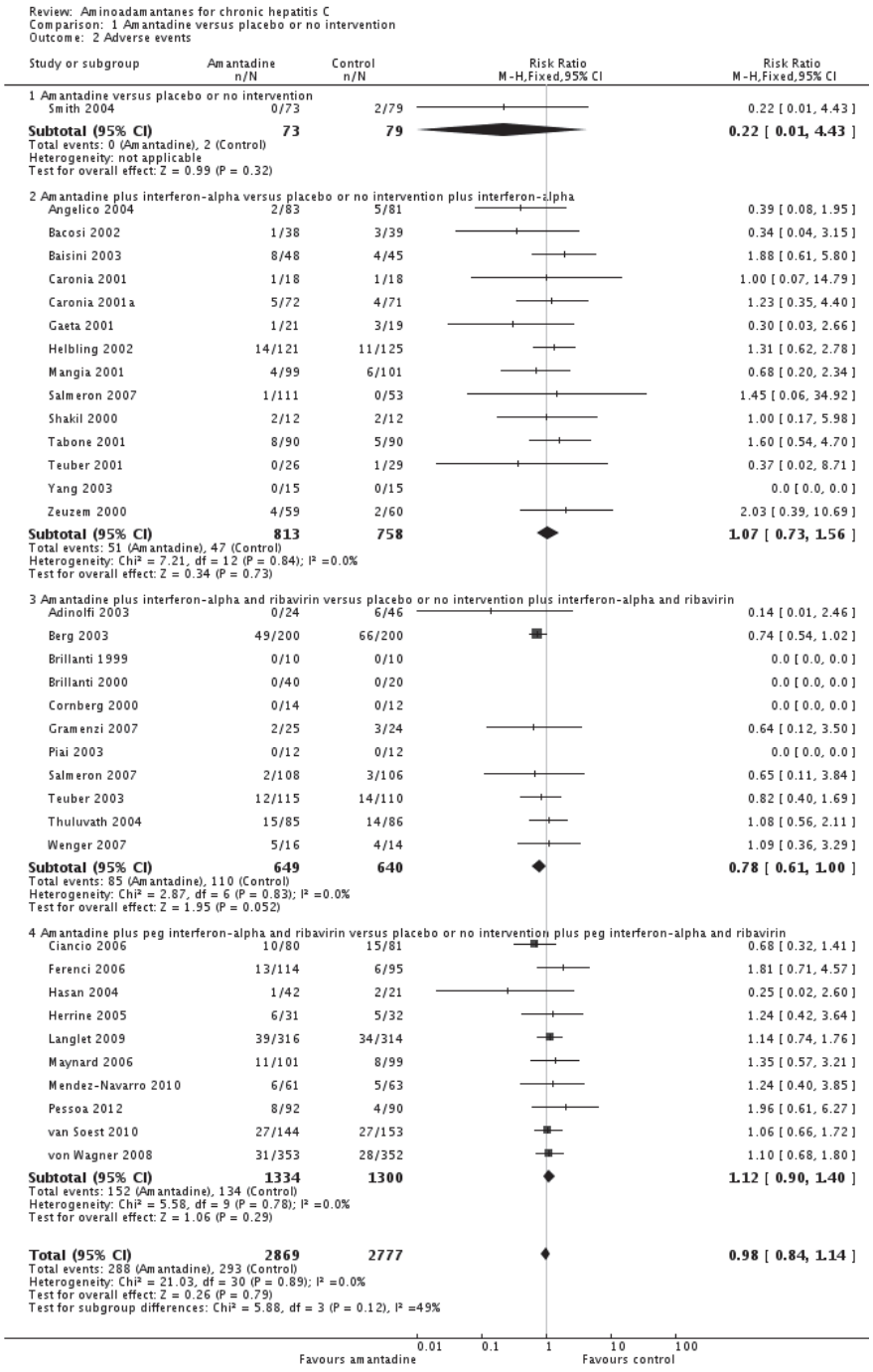
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality or liver-related morbidity	32	4617	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.38, 2.17]
1.1 Amantadine versus placebo or no intervention	1	152	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.01, 8.71]
1.2 Amantadine plus interferon-alpha versus placebo or no intervention plus interferon-alpha	14	1571	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.26, 3.98]
1.3 Amantadine plus interferon-alpha and ribavirin versus placebo or no intervention plus interferon-alpha and ribavirin	10	1064	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 Amantadine plus peg interferon-alpha and ribavirin versus placebo or no intervention plus peg interferon-alpha and ribavirin	8	1830	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.28, 3.39]
2 Adverse events	35	5646	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.84, 1.14]
2.1 Amantadine versus placebo or no intervention	1	152	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.01, 4.43]
2.2 Amantadine plus interferon-alpha versus placebo or no intervention plus interferon-alpha	14	1571	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.73, 1.56]
2.3 Amantadine plus interferon-alpha and ribavirin versus placebo or no intervention plus interferon-alpha and ribavirin	11	1289	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.61, 1.00]
2.4 Amantadine plus peg interferon-alpha and ribavirin versus placebo or no intervention plus peg interferon-alpha and ribavirin	10	2634	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.90, 1.40]
3 Failure of end of treatment virological response	30	4861	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.90, 1.00]
3.1 Amantadine plus interferon-alpha versus placebo or no intervention plus interferon-alpha	11	1129	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.88, 1.01]
3.2 Amantadine plus interferon-alpha and ribavirin versus placebo or no intervention plus interferon-alpha and ribavirin	10	1219	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.79, 0.94]
3.3 Amantadine plus peg interferon-alpha and ribavirin verus placebo or no intervention plus peg interferon-alpha and ribavirin	10	2513	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.94, 1.13]
4 Failure of sustained virological response	35	5582	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.95, 1.02]

4.1 Amantadine plus interferon-alpha versus placebo or no intervention plus interferon-alpha	13	1313	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.94, 1.04]
4.2 Amantadine plus interferon-alpha and ribavirin versus placebo or no intervention plus interferon-alpha and ribavirin	11	1294	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.83, 0.96]
4.3 Amantadine plus peg interferon-alpha and ribavirin versus placebo or no intervention plus peg interferon-alpha and ribavirin	12	2975	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.97, 1.10]
5 Failure of histological response	3	236	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.93, 1.09]
5.1 Amantadine plus interferon-alpha versus placebo or no intervention plus interferon-alpha	3	236	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.93, 1.09]
6 Failure of normalisation of ALT at end of treatment	19	2241	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.83, 0.94]
6.1 Amantadine versus placebo or no intervention	1	152	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.70, 0.94]
6.2 Amantadine plus interferon-alpha versus placebo or no intervention plus interferon-alpha	9	1018	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.87, 1.04]
6.3 Amantadine plus interferon-alpha and ribavirin versus placebo or no intervention plus interferon-alpha and ribavirin	7	808	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.70, 0.89]
6.4 Amantadine plus peg interferon-alpha and ribavirin versus placebo or no intervention plus peg interferon-alpha and ribavirin	2	263	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.78, 1.18]
7 Failure of normalisation of ALT at end of follow-up	21	3744	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.91, 1.00]
7.1 Amantadine plus interferon-alpha versus placebo or no intervention plus interferon-alpha	8	994	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.88, 1.01]
7.2 Amantadine plus interferon-alpha and ribavirin versus placebo or no intervention plus interferon-alpha and ribavirin	6	784	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.74, 0.92]
7.3 Amantadine plus peg interferon-alpha and ribavirin versus placebo or no intervention plus peg interferon-alpha and ribavirin	7	1966	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.95, 1.11]

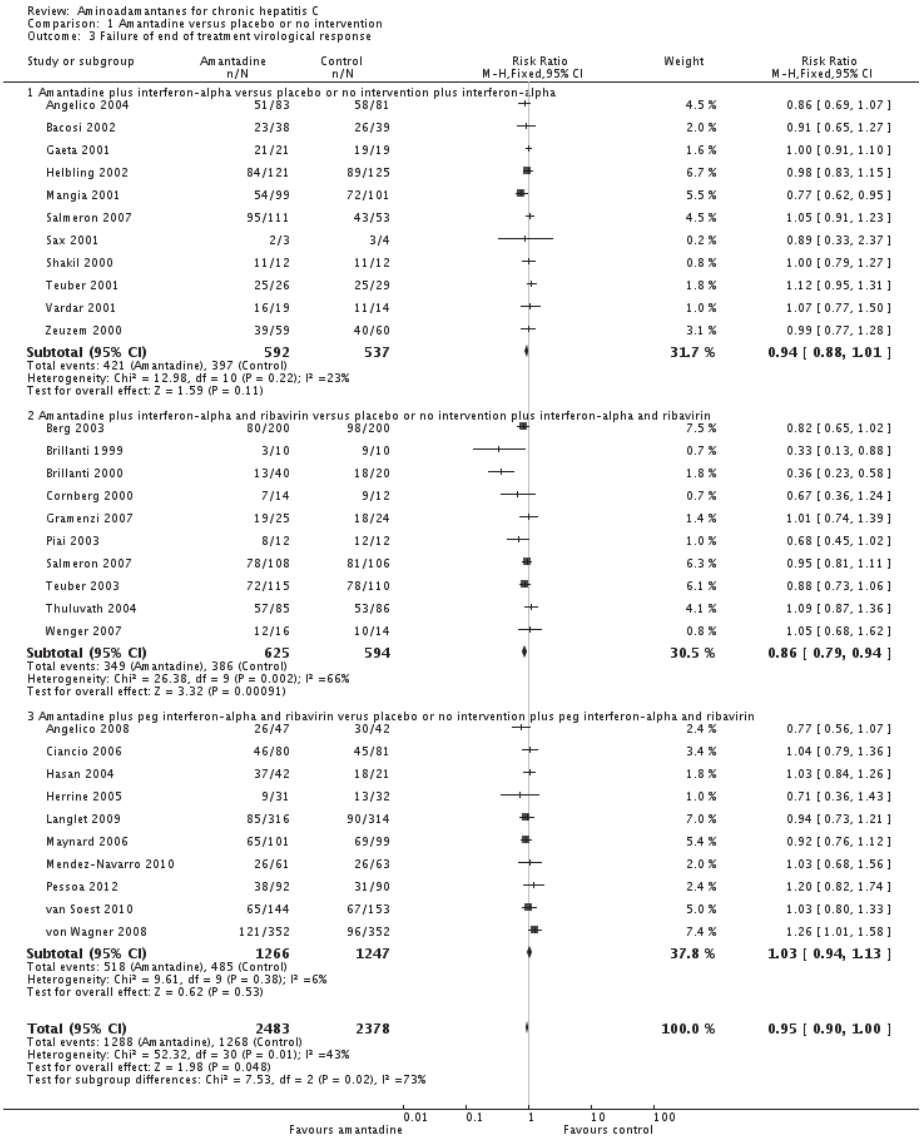
Analysis 1.1. Comparison 1 Amantadine versus placebo or no intervention, Outcome 1 All-cause mortality or liver-related morbidity.



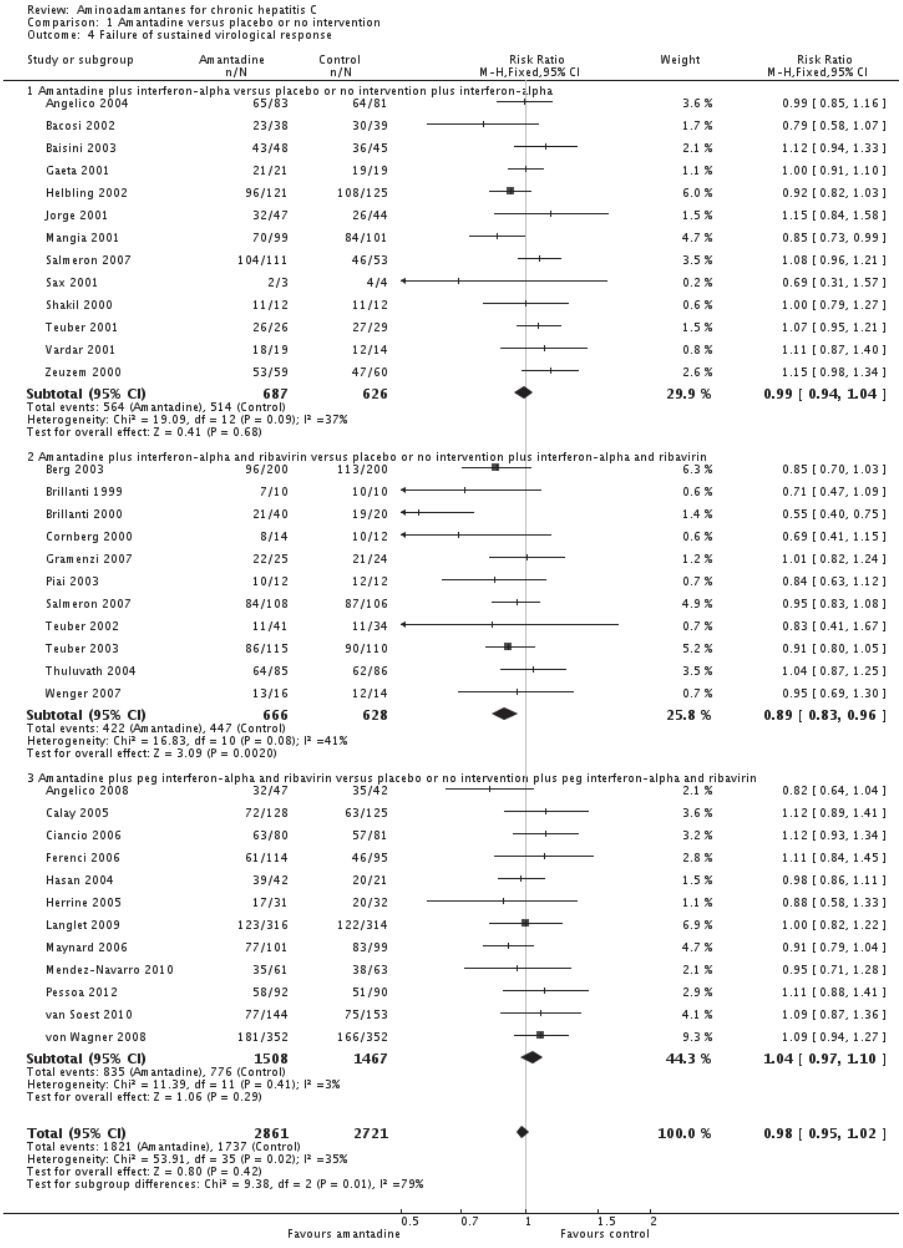
Analysis 1.2. Comparison 1 Amantadine versus placebo or no intervention, Outcome 2 Adverse events.



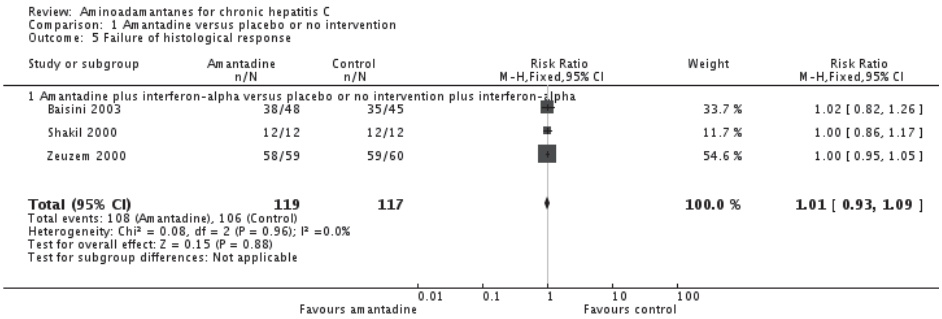
Analysis 1.3. Comparison 1 Amantadine versus placebo or no intervention, Outcome 3 Failure of end of treatment virological response.



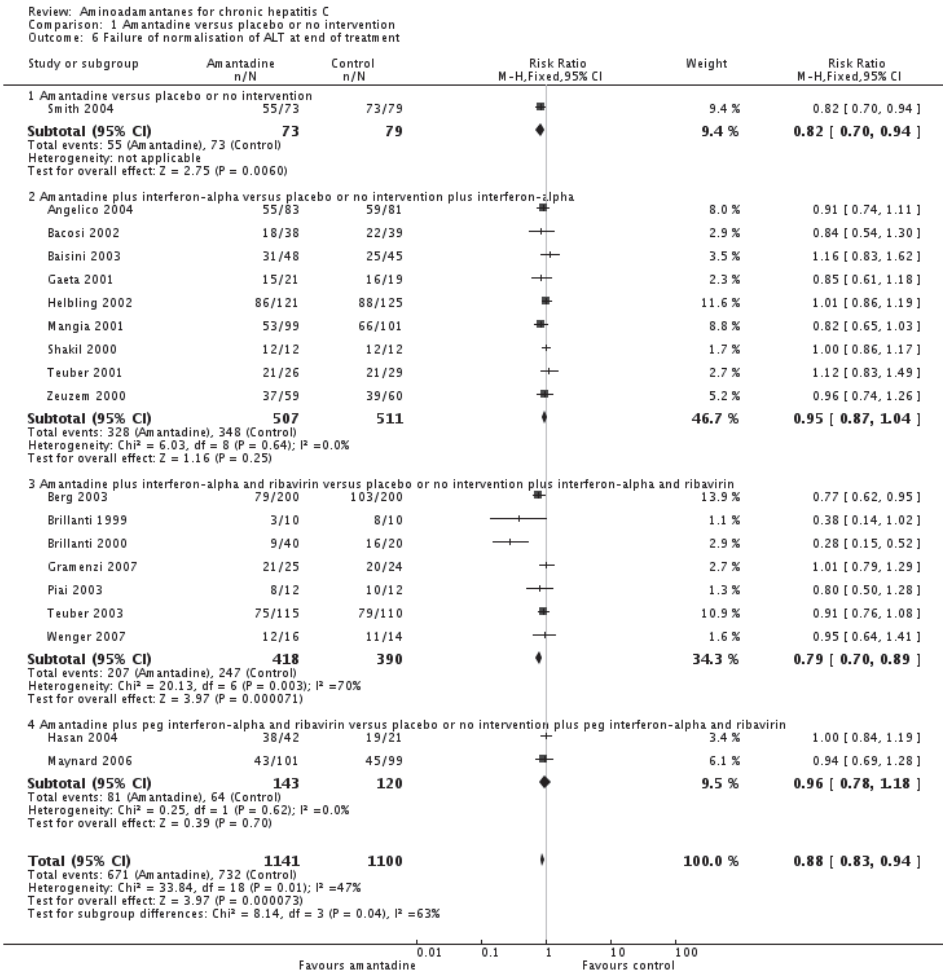
Analysis 1.4. Comparison 1 Amantadine versus placebo or no intervention, Outcome 4 Failure of sustained virological response.



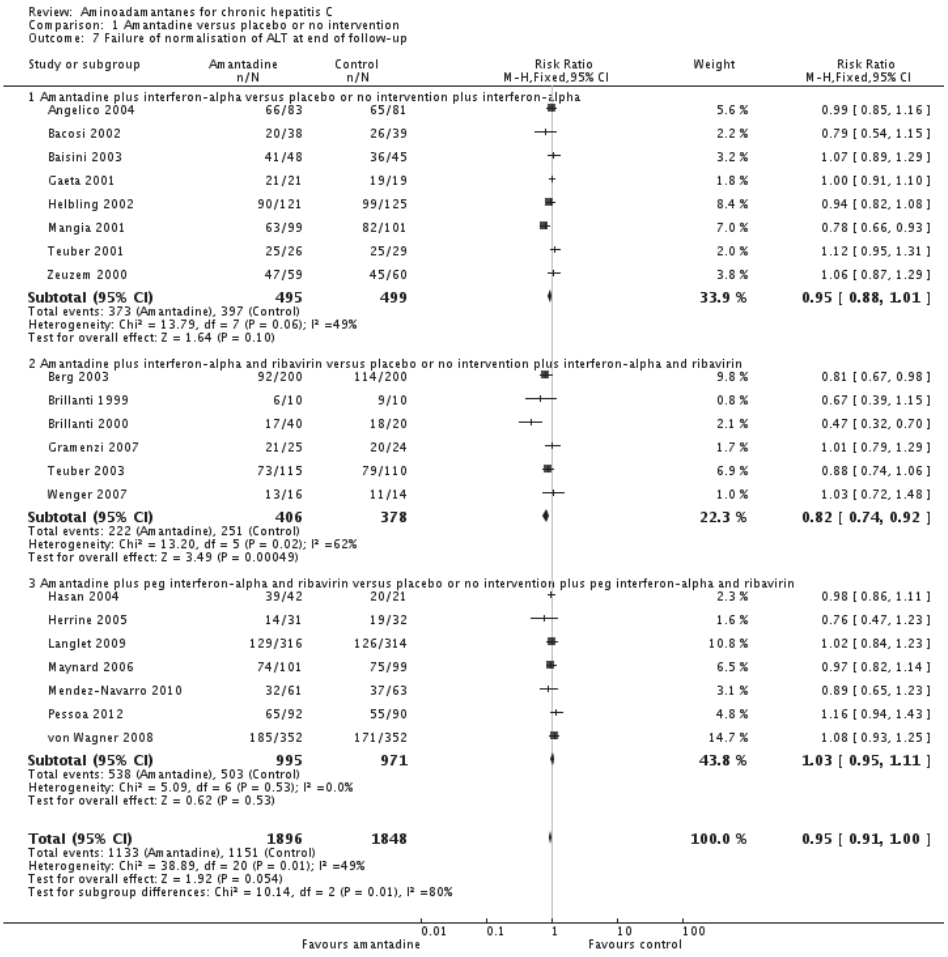
Analysis 1.5. Comparison 1 Amantadine versus placebo or no intervention, Outcome 5 Failure of histological response.



Analysis 1.6. Comparison 1 Amantadine versus placebo or no intervention, Outcome 6 Failure of normalisation of ALT at end of treatment.



Analysis 1.7. Comparison 1 Amantadine versus placebo or no intervention, Outcome 7 Failure of normalisation of ALT at end of follow-up.

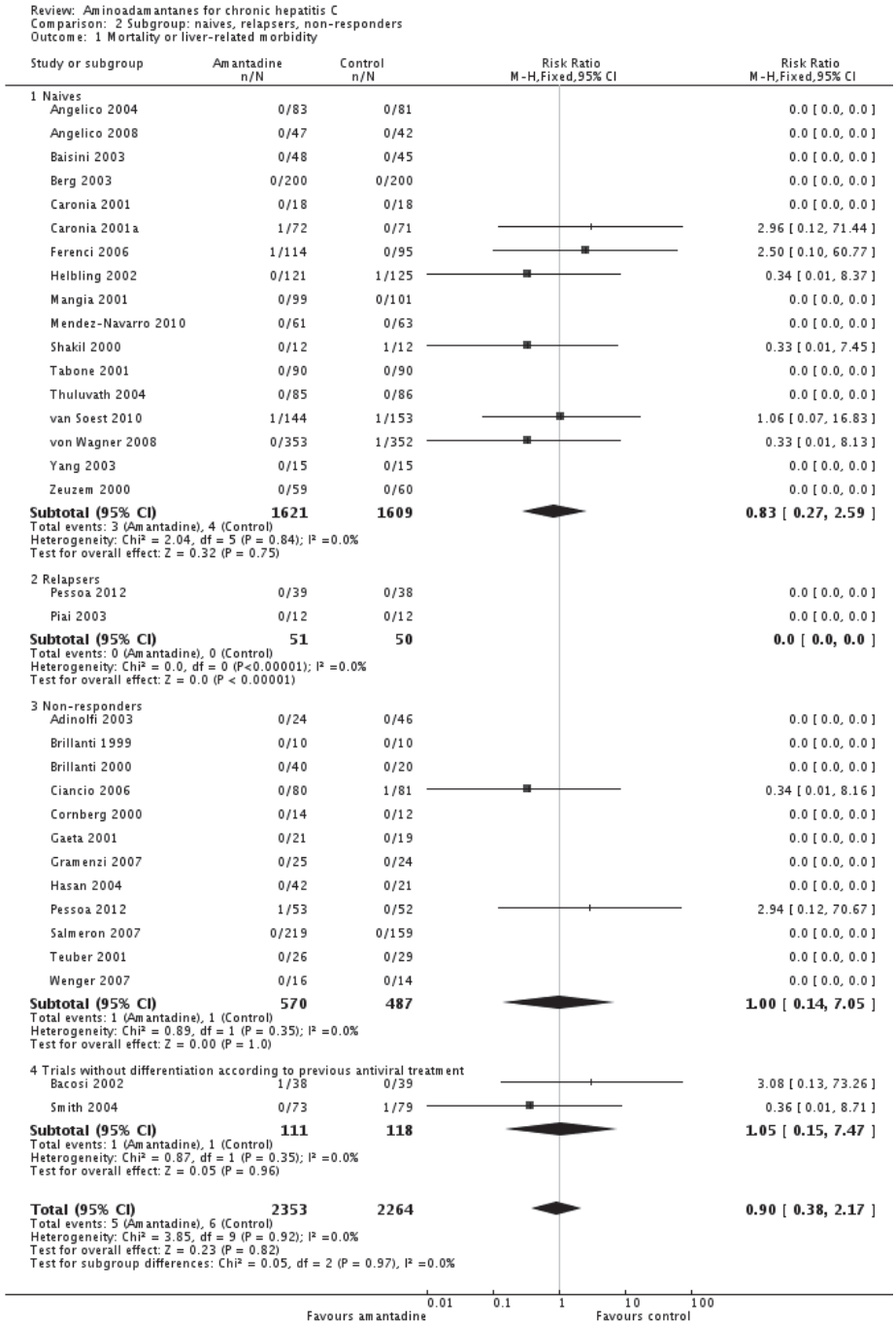


Comparison 2. Subgroup: naives, relapsers, non-responders

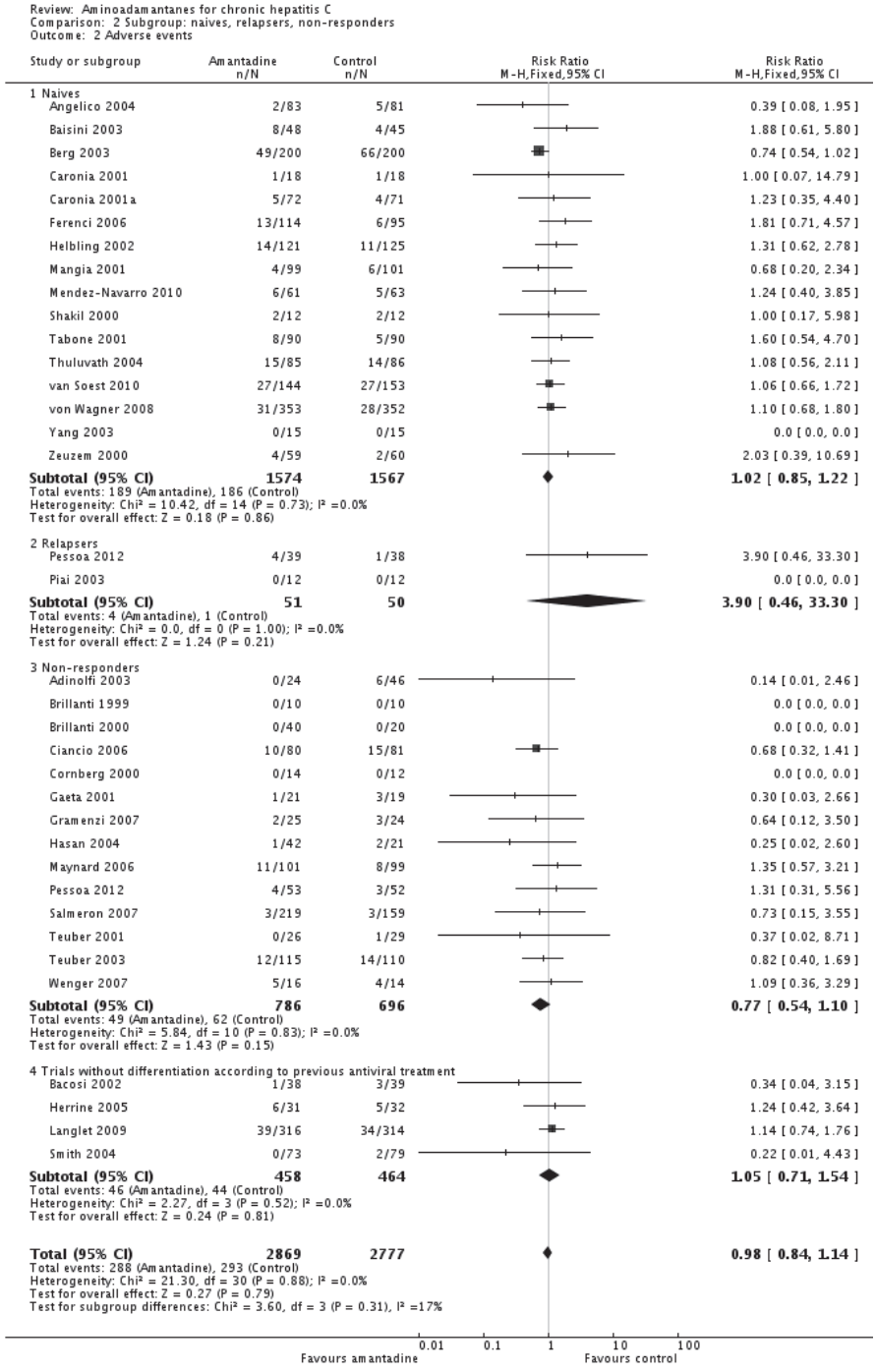
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality or liver-related morbidity	32	4617	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.38, 2.17]
1.1 Naives	17	3230	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.27, 2.59]
1.2 Relapsers	2	101	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Non-responders	12	1057	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.14, 7.05]
1.4 Trials without differentiation according to previous antiviral treatment	2	229	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.15, 7.47]
2 Adverse events	35	5646	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.84, 1.14]
2.1 Naives	16	3141	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.85, 1.22]
2.2 Relapsers	2	101	Risk Ratio (M-H, Fixed, 95% CI)	3.90 [0.46, 33.30]
2.3 Non-responders	14	1482	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.54, 1.10]
2.4 Trials without differentiation according to previous antiviral treatment	4	922	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.71, 1.54]
3 Failure of sustained virological response	35	5582	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.95, 1.02]
3.1 Naives	17	3804	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.96, 1.06]
3.2 Relapsers	4	219	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.71, 1.21]
3.3 Non-responders	13	1412	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.92, 1.02]
3.4 Trials without differentiation according to previous antiviral treatment	3	147	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.64, 1.03]
4 Failure of end of treatment virological response	30	4861	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.91, 1.00]
4.1 Naives	12	2571	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.90, 1.04]
4.2 Relapsers	2	101	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.49, 1.23]
4.3 Non-responders	13	1412	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.89, 1.02]
4.4 Trials without differentiation according	4	777	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.75, 1.11]

to previous antiviral treatment				
5 Failure of histological response	3	236	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.93, 1.09]
5.1 Naives	3	236	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.93, 1.09]
6 Failure of normalisation of ALT at end of treatment	19	2241	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.83, 0.94]
6.1 Naives	7	1246	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.83, 0.99]
6.2 Relapsers	1	24	Risk Ratio (M-H, Fixed, 95% CI)	0.8 [0.50, 1.28]
6.3 Non-responders	9	742	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.79, 0.97]
6.4 Trials without differentiation according to previous antiviral treatment	2	229	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.71, 0.96]
7 Failure of normalisation of ALT at end of follow-up	21	3744	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.91, 1.00]
7.1 Naives	8	2050	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.89, 1.02]
7.2 Relapsers	1	77	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.66, 1.43]
7.3 Non-responders	10	847	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.88, 1.03]
7.4 Trials without differentiation according to previous antiviral treatment	3	770	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.81, 1.12]

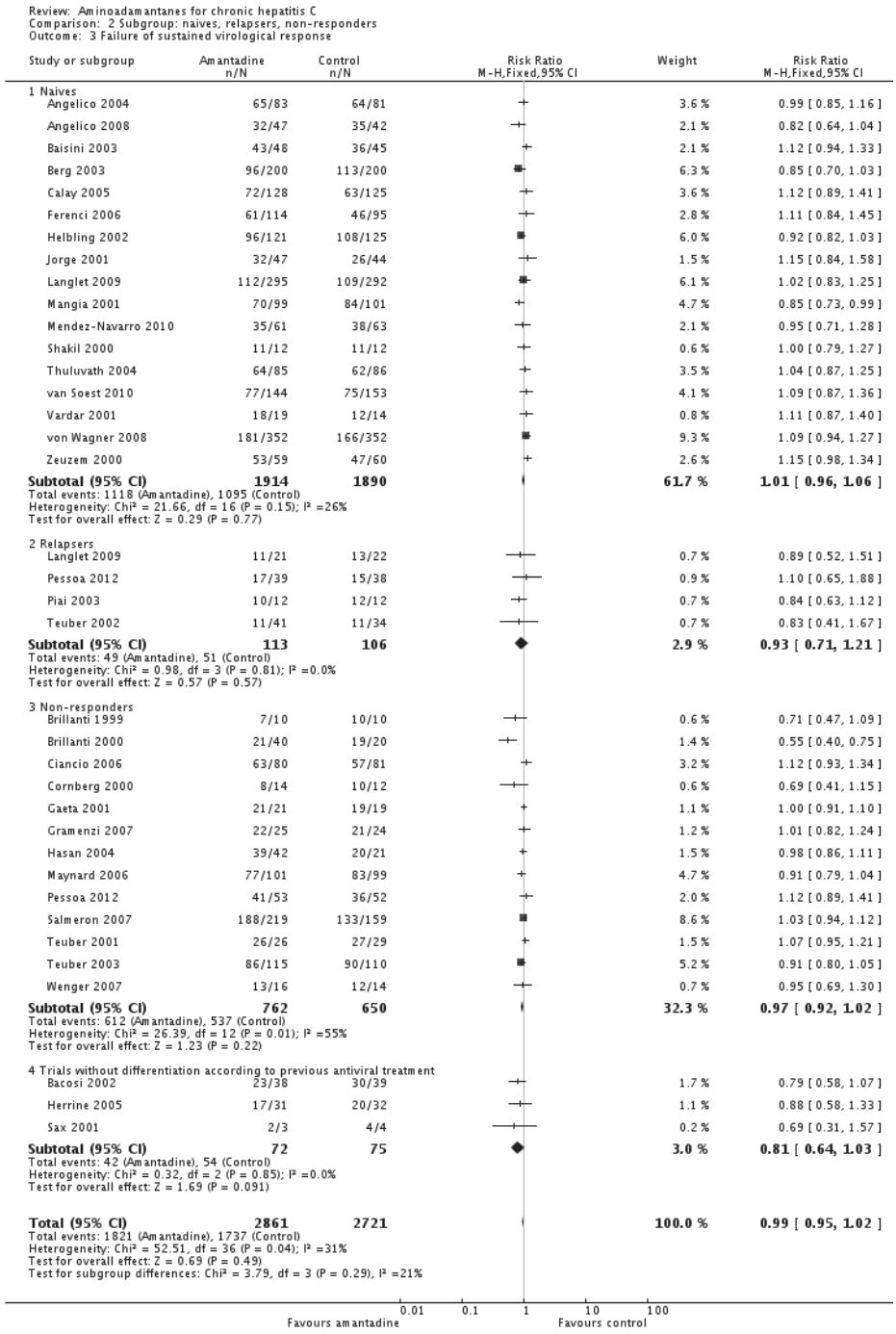
Analysis 2.1. Comparison 2 Subgroup: naives, relapsers, non-responders, Outcome 1 Mortality or liver-related morbidity.



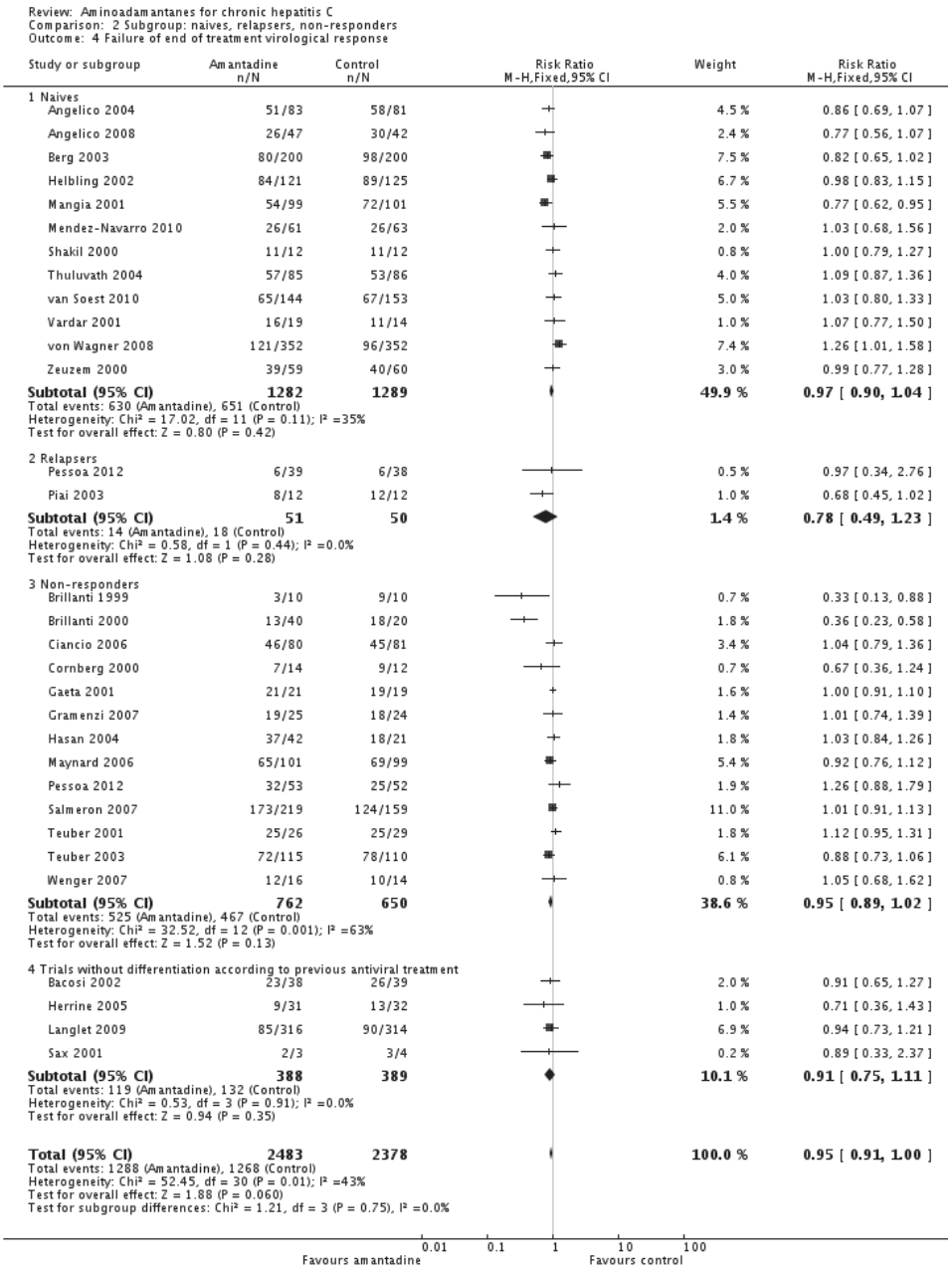
Analysis 2.2. Comparison 2 Subgroup: naives, relapsers, non-responders, Outcome 2 Adverse events.



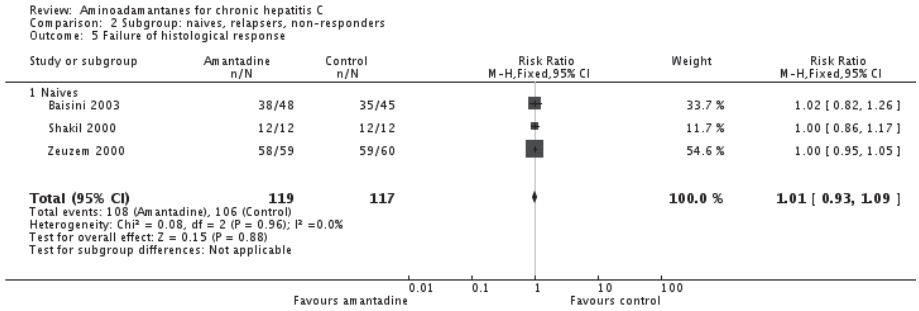
Analysis 2.3. Comparison 2 Subgroup: naives, relapsers, non-responders, Outcome 3 Failure of sustained virological response.



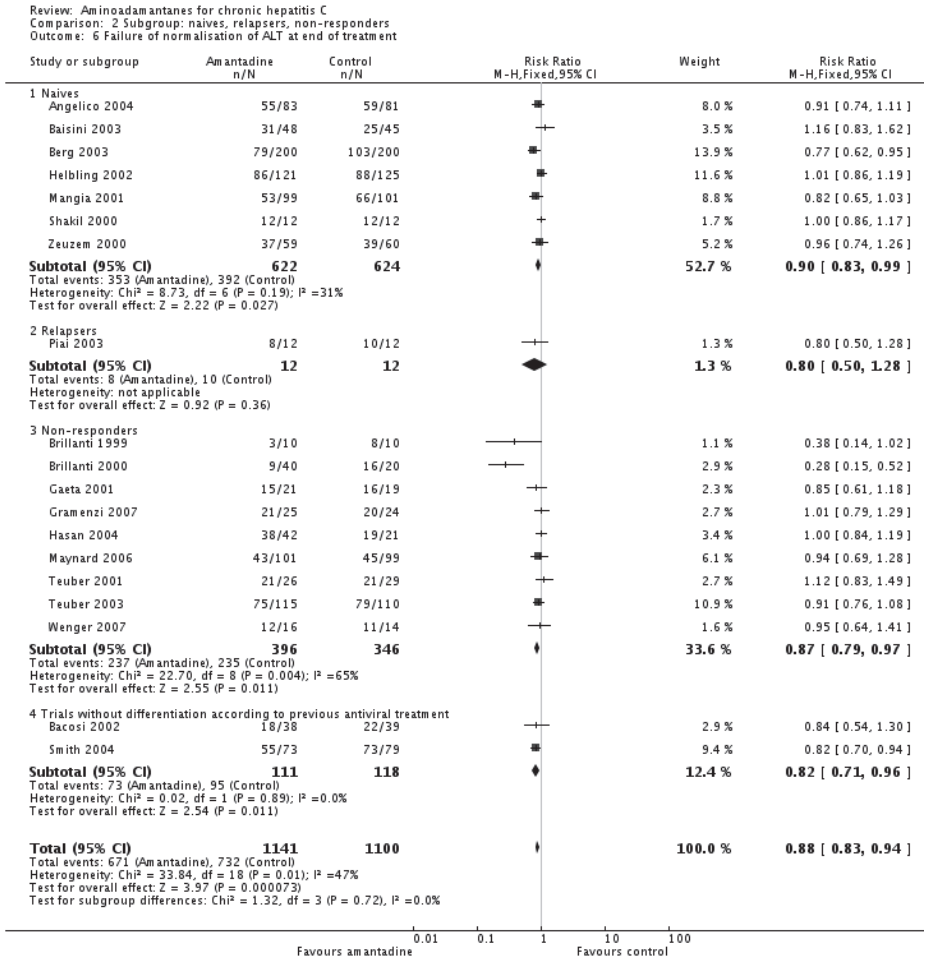
Analysis 2.4. Comparison 2 Subgroup: naives, relapsers, non-responders, Outcome 4 Failure of end of treatment virological response.



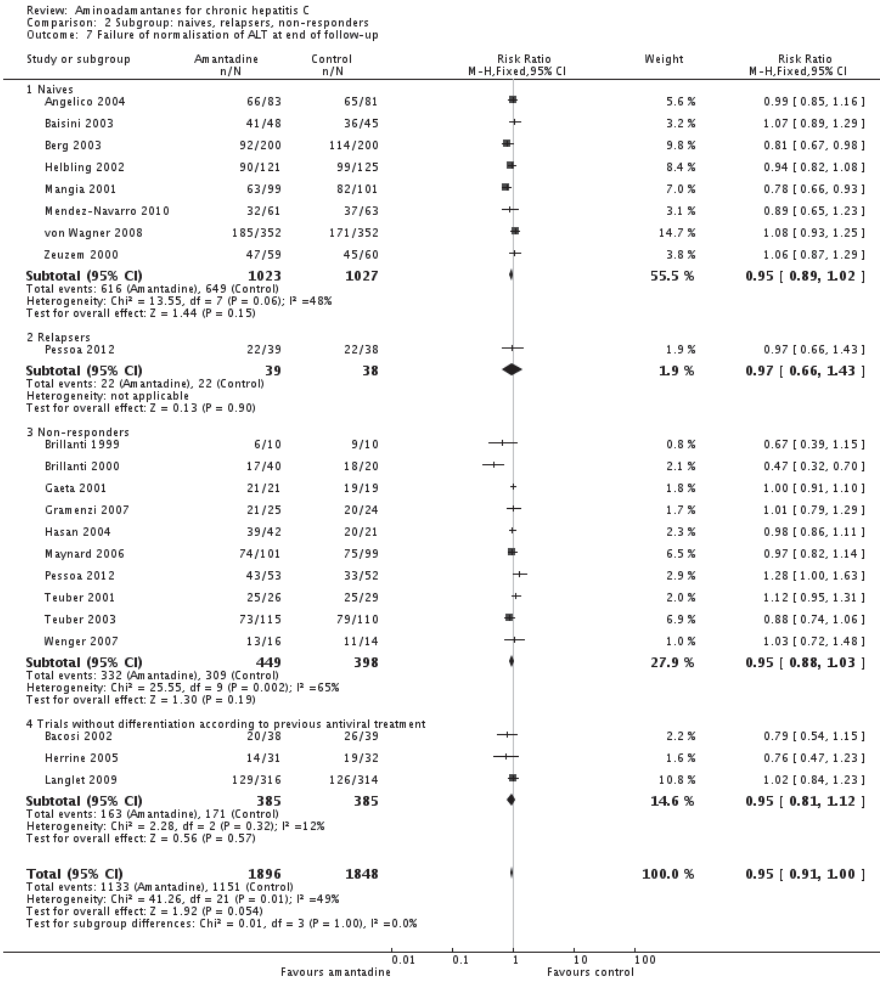
Analysis 2.5. Comparison 2 Subgroup: naives, relapsers, non-responders, Outcome 5 Failure of histological response.



Analysis 2.6. Comparison 2 Subgroup: naives, relapsers, non-responders, Outcome 6 Failure of normalisation of ALT at end of treatment.



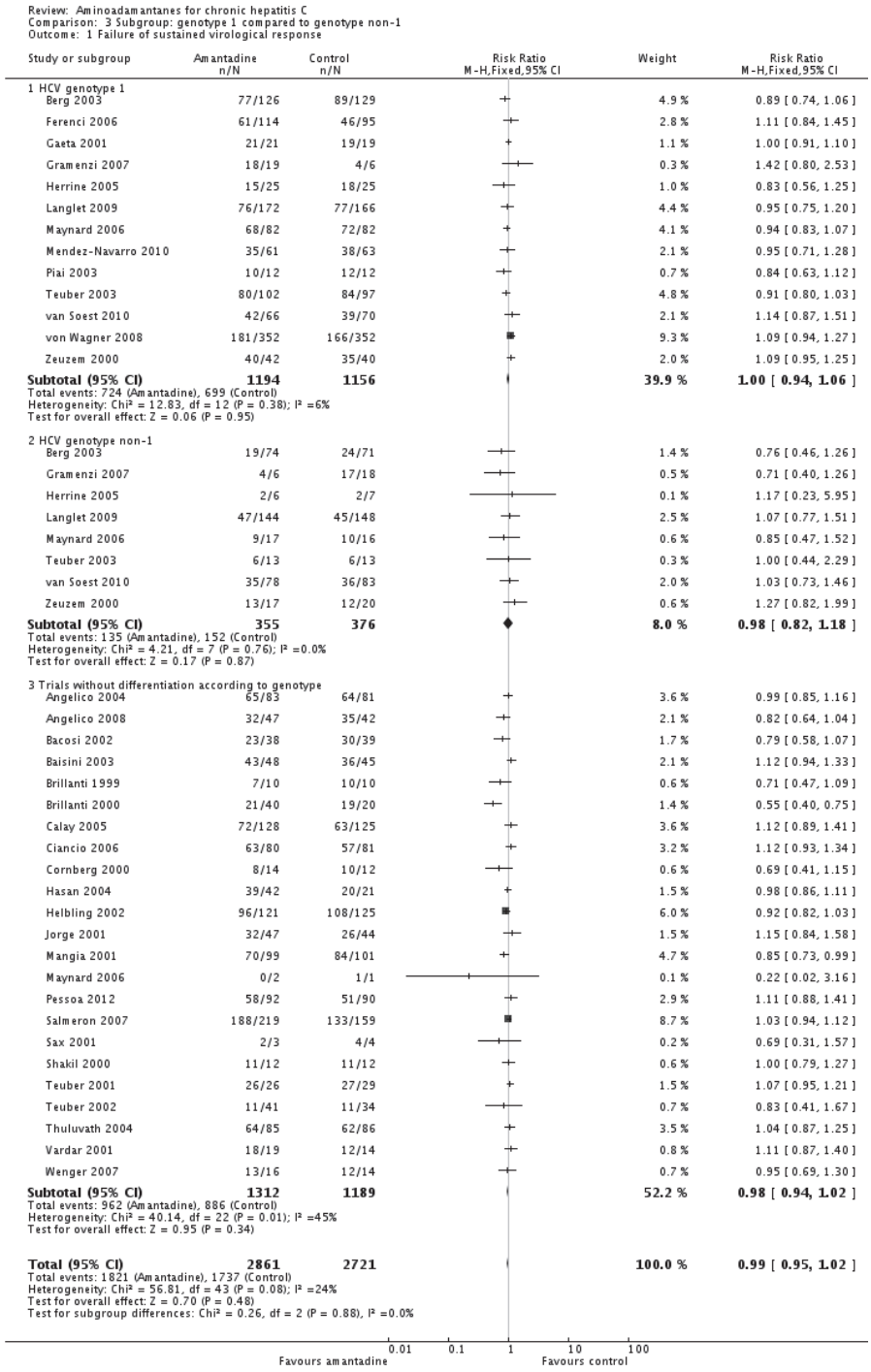
Analysis 2.7. Comparison 2 Subgroup: naives, relapsers, non-responders, Outcome 7 Failure of normalisation of ALT at end of follow-up.



Comparison 3. Subgroup: genotype 1 compared to genotype non-1

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Failure of sustained virological response	35	5582	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.95, 1.02]
1.1 HCV genotype 1	13	2350	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.94, 1.06]
1.2 HCV genotype non-1	8	731	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.82, 1.18]
1.3 Trials without differentiation according to genotype	23	2501	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.94, 1.02]

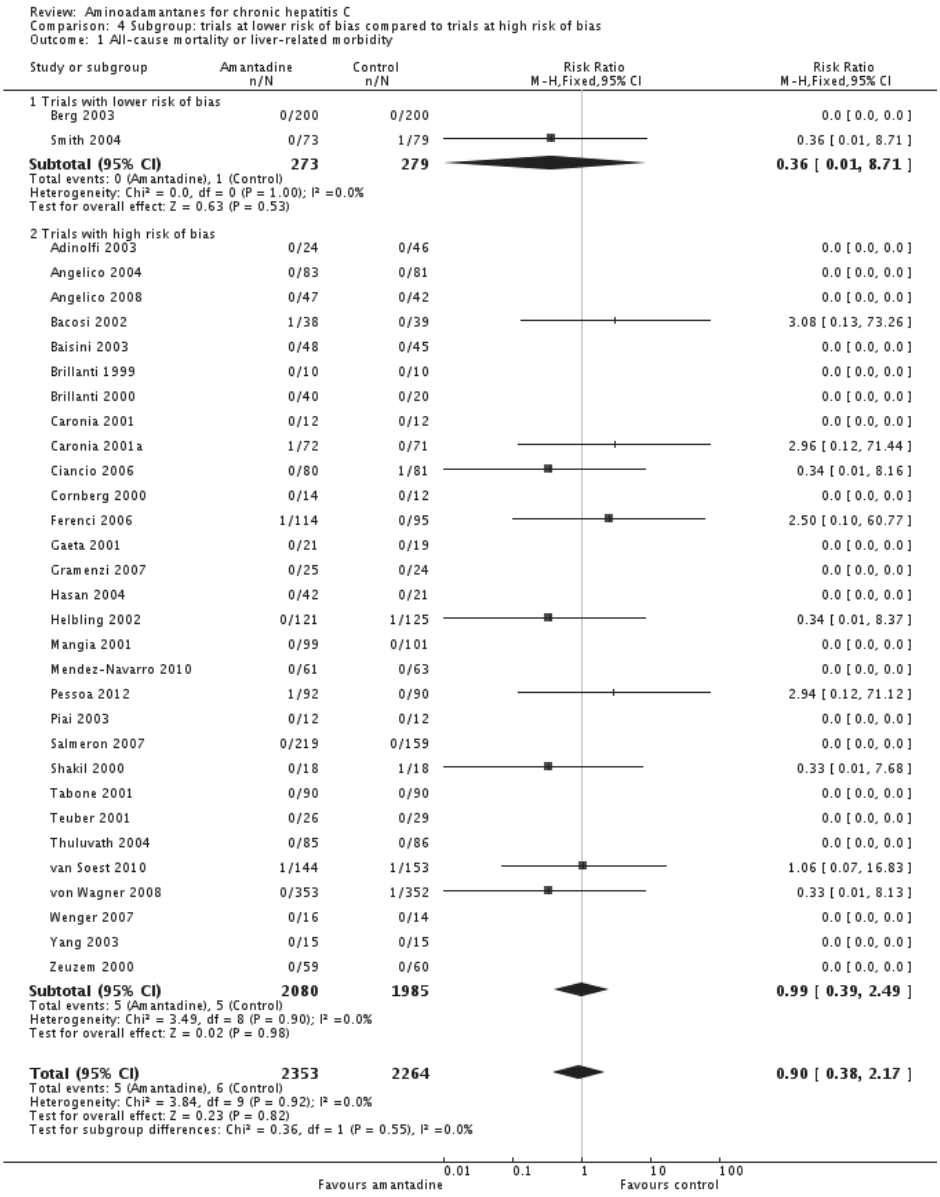
Analysis 3.1. Comparison 3 Subgroup: genotype 1 compared to genotype non-1, Outcome 1 Failure of sustained virological response.



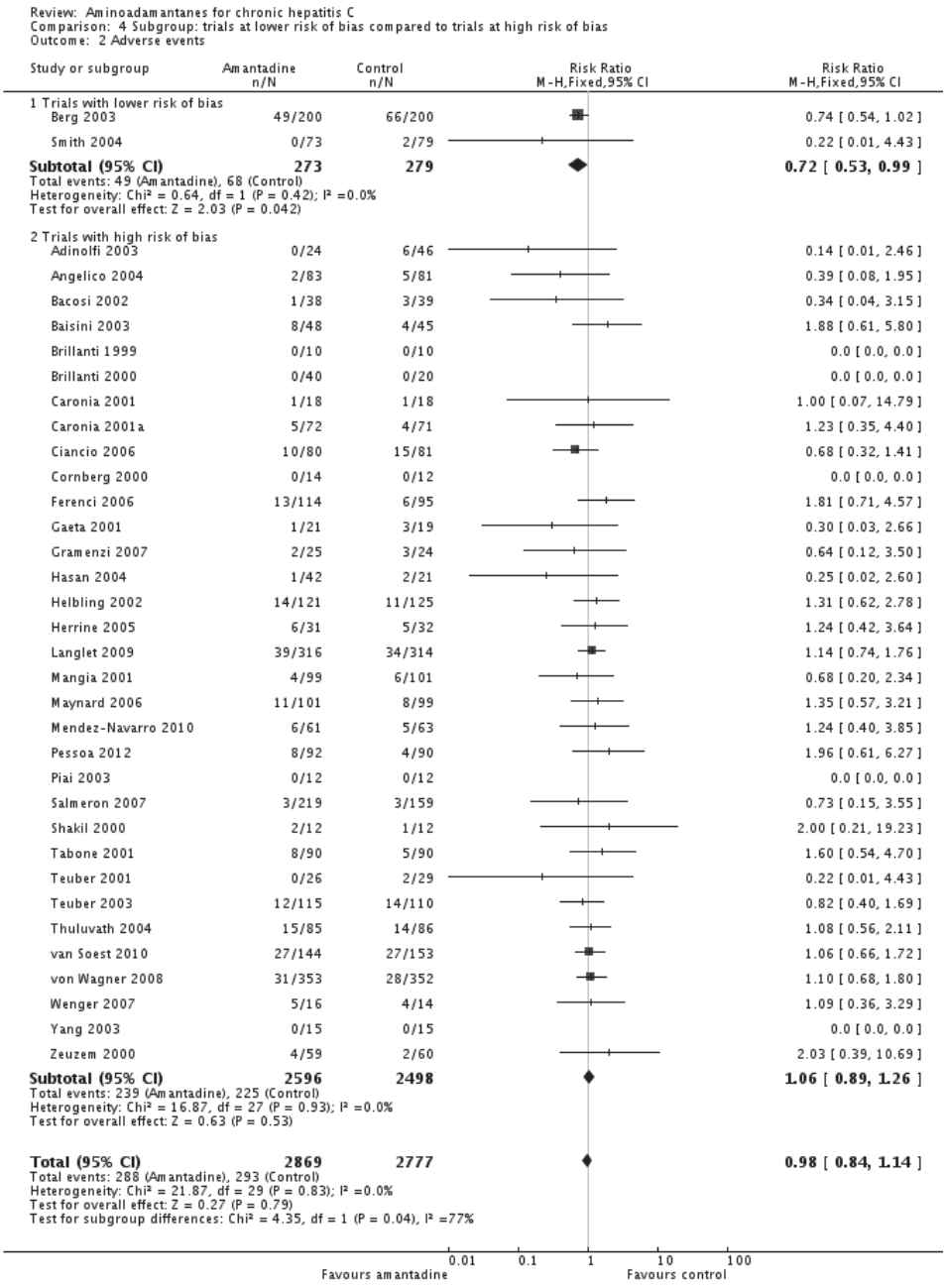
Comparison 4. Subgroup: trials at lower risk of bias compared to trials at high risk of bias

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality or liver-related morbidity	32	4617	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.38, 2.17]
1.1 Trials with lower risk of bias	2	552	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.01, 8.71]
1.2 Trials with high risk of bias	30	4065	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.39, 2.49]
2 Adverse events	35	5646	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.84, 1.14]
2.1 Trials with lower risk of bias	2	552	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.53, 0.99]
2.2 Trials with high risk of bias	33	5094	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.89, 1.26]
3 Failure of sustained virological response	35	5582	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.95, 1.02]
3.1 Trials with lower risk of bias	1	400	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.70, 1.03]
3.2 Trials with high risk of bias	34	5182	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.96, 1.03]
4 Failure of end of treatment virological response	30	4861	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.91, 1.00]
4.1 Trials with lower risk of bias	1	400	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.65, 1.02]
4.2 Trials with high risk of bias	29	4461	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.92, 1.01]
5 Failure of histological response	3	236	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.93, 1.09]
5.1 Trials with high risk of bias	3	236	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.93, 1.09]
6 Failure of normalisation of ALT at end of treatment	19	2241	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.83, 0.94]
6.1 Trials with lower risk of bias	2	552	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.68, 0.91]
6.2 Trials with high risk of bias	17	1689	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.85, 0.98]
7 Failure of normalisation of ALT at end of follow-up	21	3744	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.91, 1.00]
7.1 Trials with lower risk of bias	1	400	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.67, 0.98]
7.2 Trials with high risk of bias	20	3344	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.92, 1.02]

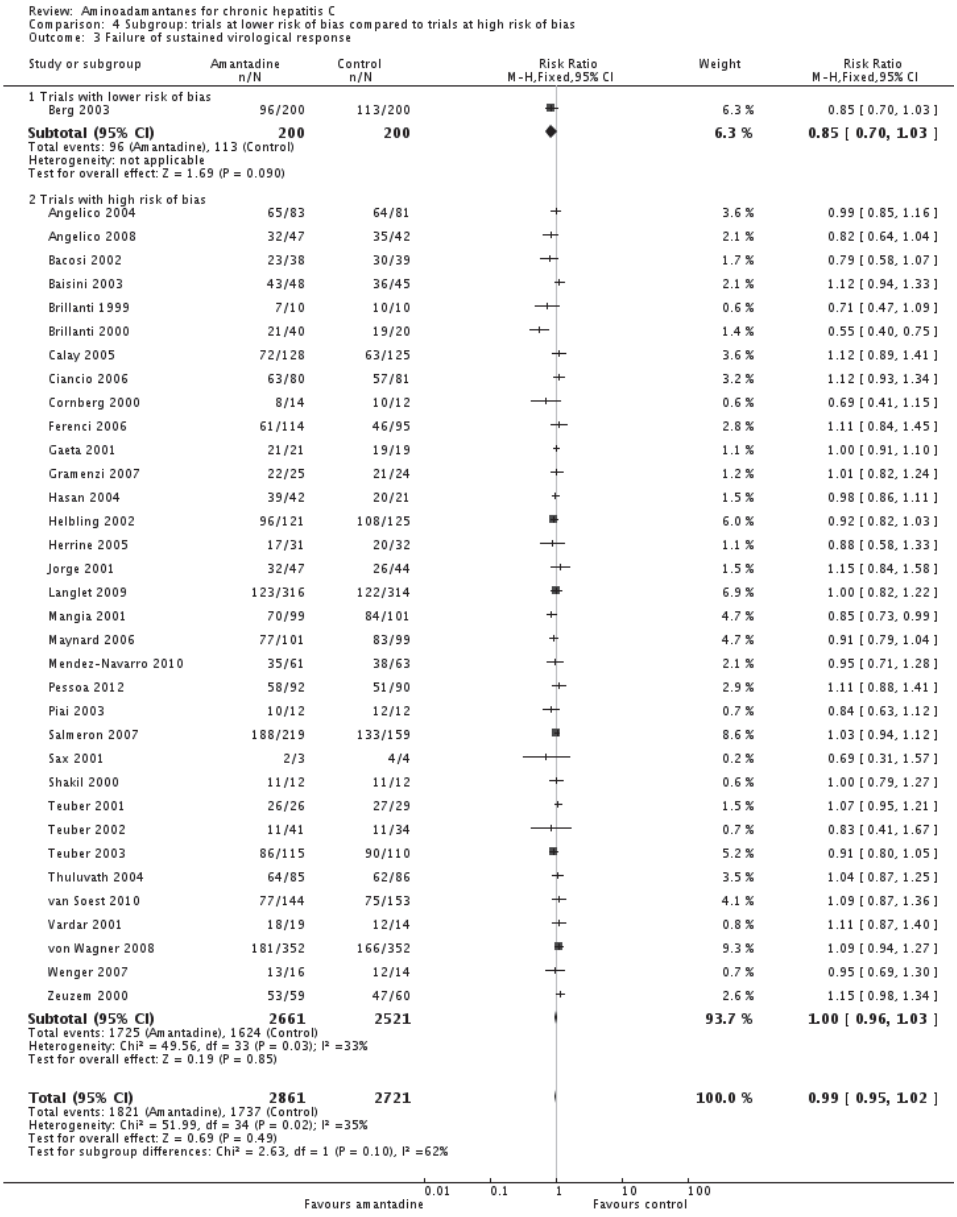
Analysis 4.1. Comparison 4 Subgroup: trials at lower risk of bias compared to trials at high risk of bias, Outcome 1 All-cause mortality or liver-related morbidity.



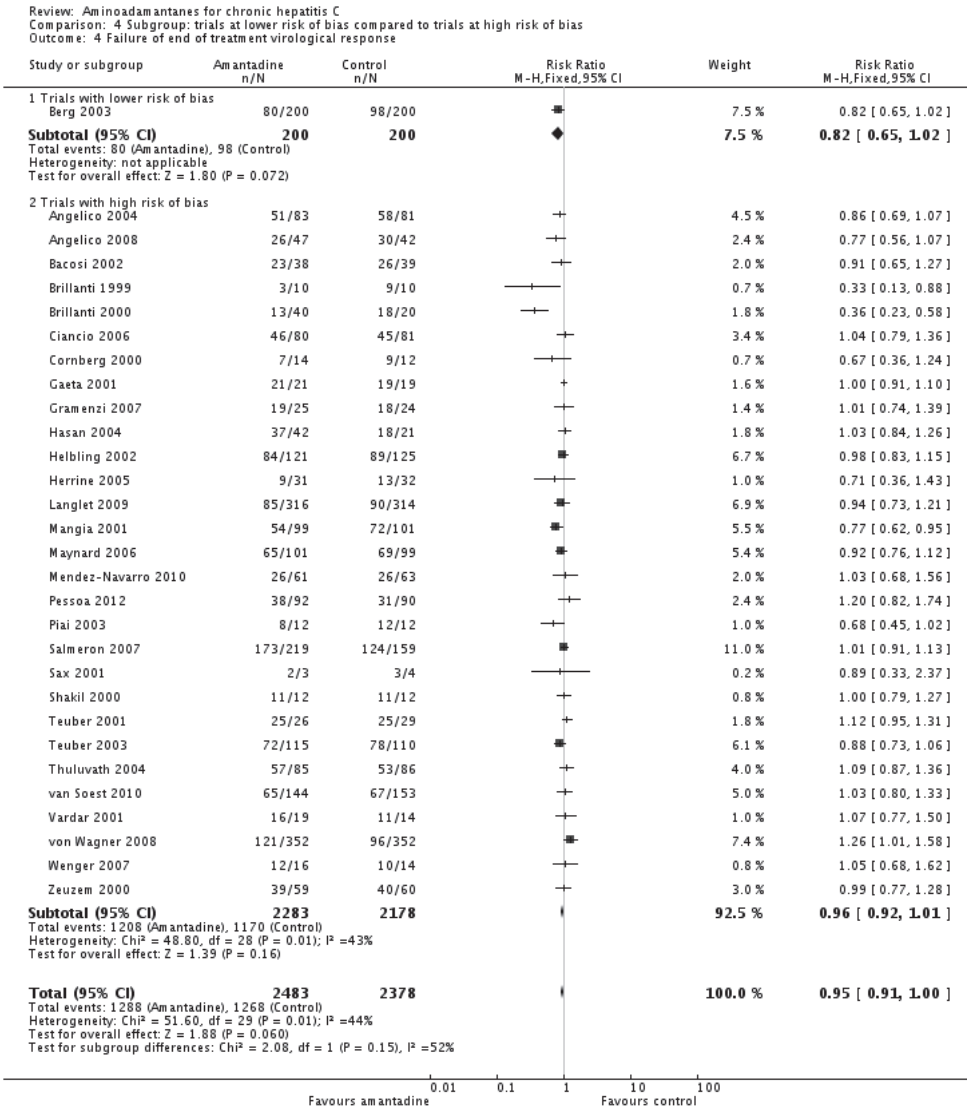
Analysis 4.2. Comparison 4 Subgroup: trials at lower risk of bias compared to trials at high risk of bias, Outcome 2 Adverse events.



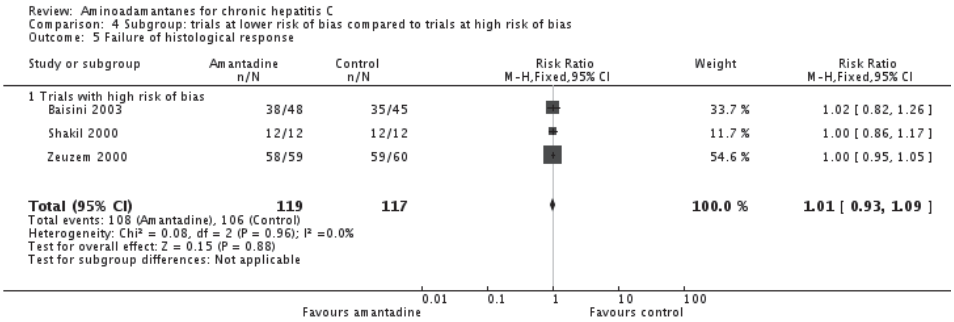
Analysis 4.3. Comparison 4 Subgroup: trials at lower risk of bias compared to trials at high risk of bias, Outcome 3 Failure of sustained virological response.



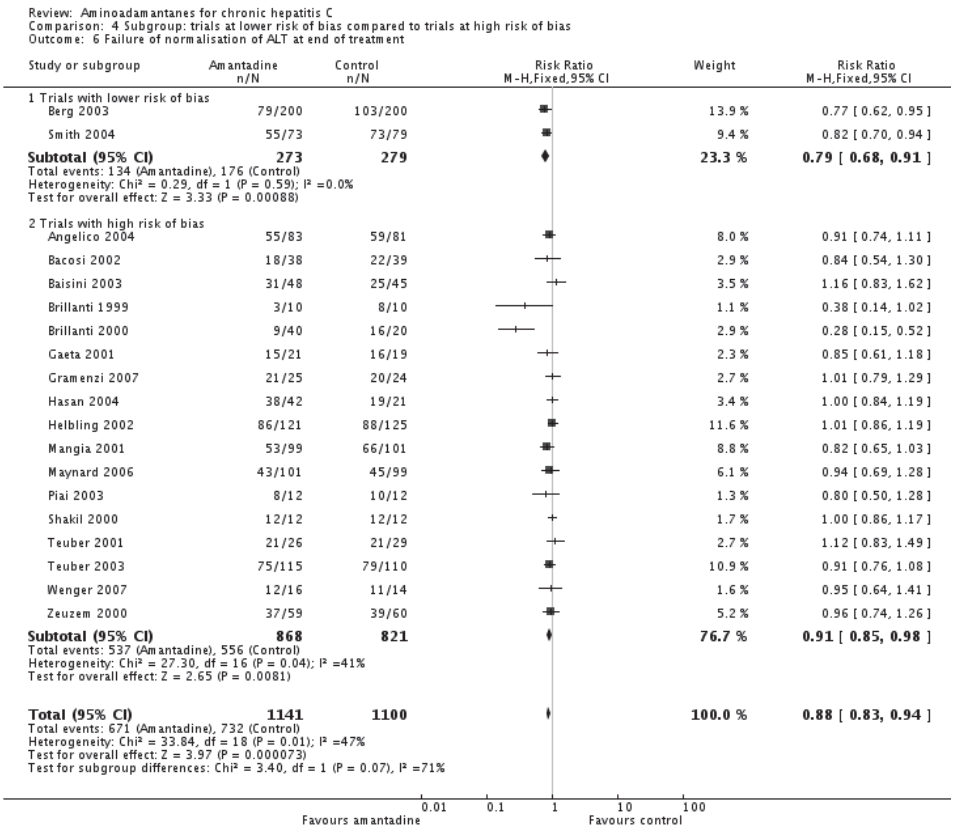
Analysis 4.4. Comparison 4 Subgroup: trials at lower risk of bias compared to trials at high risk of bias, Outcome 4 Failure of end of treatment virological response.



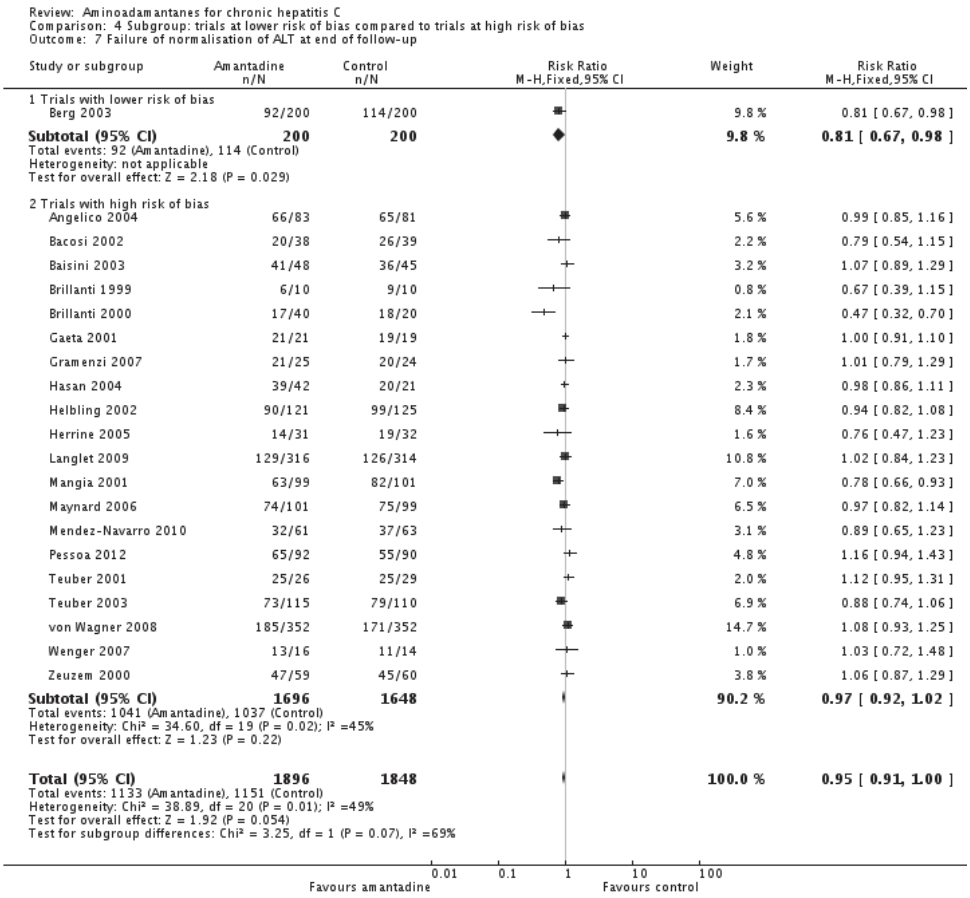
Analysis 4.5. Comparison 4 Subgroup: trials at lower risk of bias compared to trials at high risk of bias, Outcome 5 Failure of histological response.



Analysis 4.6. Comparison 4 Subgroup: trials at lower risk of bias compared to trials at high risk of bias, Outcome 6 Failure of normalisation of ALT at end of treatment.



Analysis 4.7. Comparison 4 Subgroup: trials at lower risk of bias compared to trials at high risk of bias, Outcome 7 Failure of normalisation of ALT at end of follow-up.

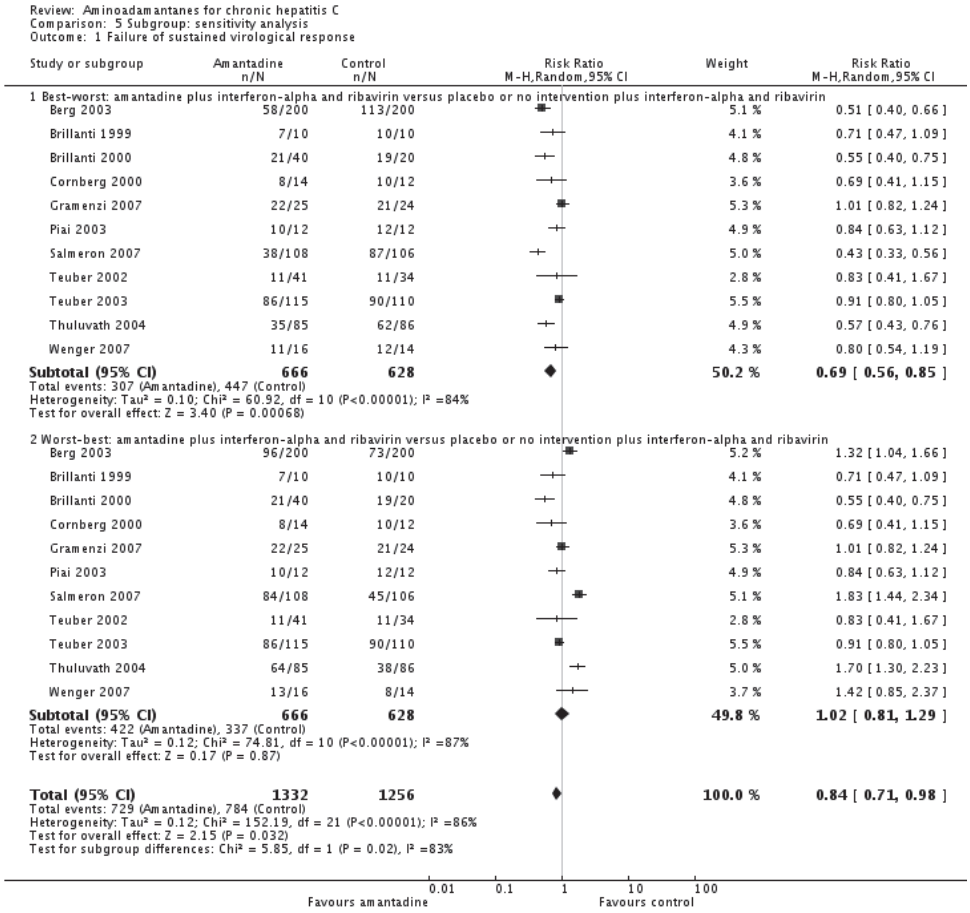


Comparison 5. Subgroup: sensitivity analysis

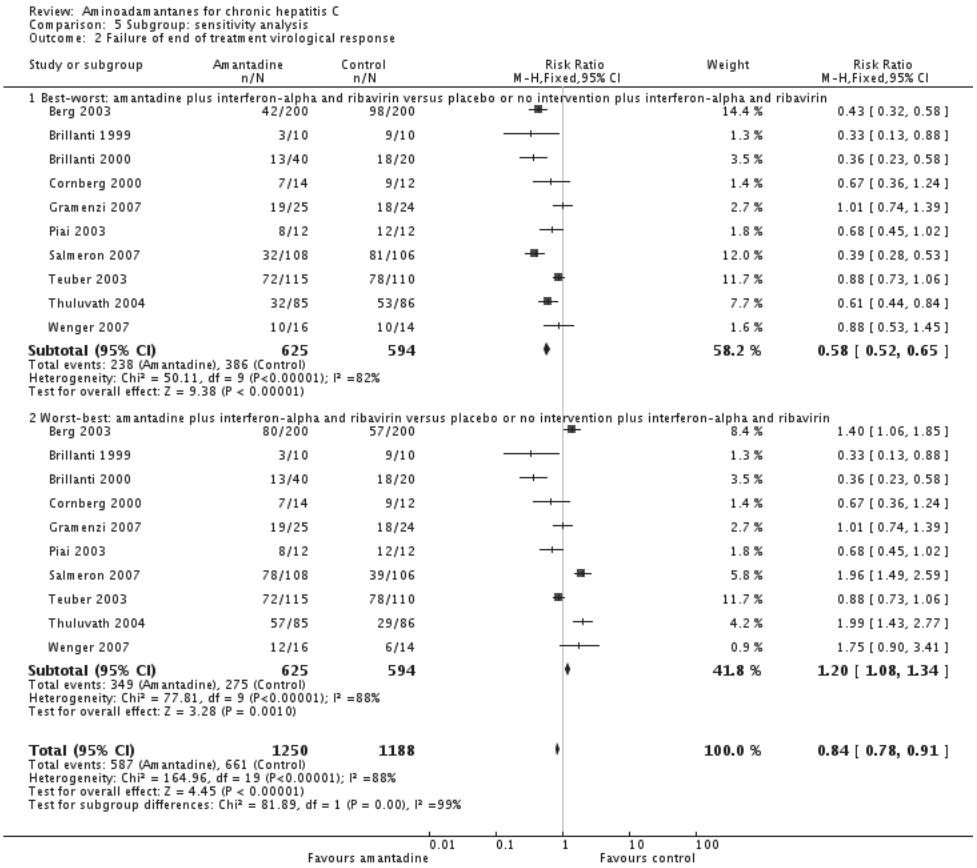
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Failure of sustained virological response	11	2588	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.71, 0.98]
1.1 Best-worst: amantadine plus interferon-alpha and ribavirin versus placebo or no intervention plus interferon-alpha and ribavirin	11	1294	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.56, 0.85]
1.2 Worst-best: amantadine plus interferon-alpha and ribavirin versus placebo or no intervention plus interferon-alpha and ribavirin	11	1294	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.81, 1.29]

2 Failure of end of treatment virological response	10	2438	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.78, 0.91]
2.1 Best-worst: amantadine plus interferon-alpha and ribavirin versus placebo or no intervention plus interferon-alpha and ribavirin	10	1219	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.52, 0.65]
2.2 Worst-best: amantadine plus interferon-alpha and ribavirin versus placebo or no intervention plus interferon-alpha and ribavirin	10	1219	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [1.08, 1.34]

Analysis 5.1. Comparison 5 Subgroup: sensitivity analysis, Outcome 1 Failure of sustained virological response.



Analysis 5.2. Comparison 5 Subgroup: sensitivity analysis, Outcome 2 Failure of end of treatment virological response.



Appendices

Appendix 1. Search strategies

Database	Time span	Search strategy
Cochrane Hepato-Biliary Group Controlled Trials Register	1996 to December 2013	(adaman* OR amantadin* OR symmetrel OR symandin* OR rimantadin* OR flumadin* OR methenamin*) AND ('hepatitis C' OR 'hep C' OR HCV)
Cochrane Central Register of Controlled Trials (CENTRAL) CENTRAL 2013, Issue 11 of 12, in *The Cochrane Library* (Wiley)	1995 to Issue 11 of 12, 2013	#1 MeSH descriptor: [Adamantane] explode all trees #2 adaman* OR amantadin* OR symmetrel OR symandin* OR rimantadin* OR flumadin* OR methenamin* #3 (#1 OR #2) #4 MeSH descriptor: [Hepatitis C] explode all trees #5 hepatitis C OR hep C OR HCV #6 (#4 OR #5) #7 (#3 AND #6)

MEDLINE (Ovid SP)	1946 to December 2013	1. exp Adamantane/ 2. (adaman* or amantadin* or symmetrel or symandin* or rimantadin* or flumadin* or methenamin*).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] 3. 1 or 2 4. exp Hepatitis C/ 5. (hepatitis C or hep C or HCV).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] 6. 4 or 5 7. 3 and 6 8. (random* or blind* or placebo* or meta-analys*).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] 9. 7 and 8
EMBASE (Ovid SP)	1974 to December 2013	1. exp amantadine/ 2. exp rimantadine/ 3. (adaman* or amantadin* or symmetrel or symandin* or rimantadin* or flumadin* or methenamin*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 4. 1 or 2 or 3 5. exp hepatitis C/ 6. (hepatitis C or hep C or HCV).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 7. 5 or 6 8. 4 and 7 9. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 10. 8 and 9
Science Citation Index Expanded	1900 to December 2013	#5 #4 AND #3 #4 TS=(random* or blind* or placebo* or meta-analys*) #3 #2 AND #1 #2 TS=(hepatitis C or hep C or HCV) #1 TS=(adaman* or amantadin* or symmetrel or symandin* or rimantadin* or flumadin* or methenamin*)

Contributions of authors

ML, MB, JD, and CG were involved in the study concept and design.
ML and MB screened the literature, selected publications for inclusion and exclusion according to the eligibility criteria, extracted data, and made the 'Risk of bias' judgements.
ML, MB, and CG analysed and interpreted the data and results.
ML drafted the manuscript and performed the meta-analyses.
JD and CG were involved in critical revision of the manuscript for important intellectual content.

Declarations of interest

M.H. Lamers: no declarations of interest.
Mark Broekman: no declarations of interest.
Joost PH Drenth: no declarations of interest.
Christian Gluud: no declarations of interest.

Sources of support

Internal sources

- Radboud University Medical Center Nijmegen, Netherlands.

External sources

- The Cochrane Hepato-Biliary Group, Denmark.
  The first author, Mieke H Lamers, worked on the review for three months at the CHBG Editorial Team offices.

Differences between protocol and review

- We conducted sensitivity analysis only on the statistically significant findings and only using 'best-worse' case scenario and 'worst-best' case scenario analysis, in order to check the robustness of our analysis. We did not use 'poor outcome analysis' and 'good outcome analysis' and deleted this from our review.
- We also assessed the risk of other sources of bias (baseline imbalance bias and early stopping bias) and described this in our Characteristics of included studies table. Both may bias the individual trial, but are unlikely to bias meta-analysis. Therefore, we reported this for the individual trials, but not for our meta-analyses.

- We did not contact pharmaceutical companies who are involved in the production and assessment of aminoadamantanes.
- We included a 'Summary of findings' table.

Characteristics of studies

Characteristics of included studies [ordered by study ID]

Adinolfi 2003

Methods	Randomised clinical trial in interferon non-responder patients 12 months therapy, 12 months follow-up
Participants	**Country:** Italy 114 patients were randomized **Inclusion criteria:** chronic HCV with presence of serum HCV RNA, serum ALT levels persistently greater than 1.5 times the normal value during the follow-up period, previously received a course of recombinant or lymphoblastoid interferon-alpha 3 to 6 MU 3 times a week for at least 4 months, were considered as non-responders - that is, on no occasion had they had both serum HCV RNA clearance and normalisation of serum transaminase levels, liver biopsy in the 24 months before entering the study **Exclusion criteria:** decompensated cirrhosis, cirrhosis with signs of portal hypertension, serum HIV or HBsAg positivity, serum markers of autoimmunity with or without associated disease, alcohol intake, serum haemoglobin concentration < 12 g/dl for women and < 13 g/dl for men, white cell count < 3000 mm^3, platelet count < 100,000 mm^3, other clinically significant diseases **Amantadine group:** 24 patients, median age 50 (30 to 59) years, male/female = 16/8. Median serum ALT 105 (64 to 284) MU/mL, and a median basal viral load of 3.2 (0.8 to 28.6) eq/mL x 10^6 copies per mL. Genotype 1 (n = 17) and genotype non-1 (n = 7). Histological staging (HAI): median 5.4 (4 to 10), 8 patients cirrhosis **Control group:** 46 patients, median age 51 (30 to 60) years, male/female = 31/15. Median serum ALT 98 (62 to 308) MU/mL, and the median basal viral load of 3.0 (0.7 to 18.4) eq/mL x 10^6 copies per mL. Genotype 1 (n = 33) and genotype non-1 (n = 13). Histological staging (HAI): median 5.3 (4 to 9), 12 patients cirrhosis
Interventions	**Amantadine group:** interferon-alpha-2b sc 3 MU daily for the first 4 weeks and subsequently 3 times a week, oral ribavirin at a daily dose of 1000 mg plus oral amantadine hydrochloride 200 mg/day administered in 2 doses of 100 mg **Control group:** interferon-alpha-2b sc 3 MU daily for the first 4 weeks and subsequently 3 times a week plus oral ribavirin at a daily dose of 1000 mg
Outcomes	Mortality; liver-related morbidity; SAE; treatment discontinuation due to AE; composite outcome of number of patients with or without hepatitis C virus and ALT normalisation at end of treatment and end-of follow-up

Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not placebo-controlled
Incomplete outcome data (attrition bias) All outcomes	High risk	Drop-outs not reported separately for 3 groups
Selective reporting (reporting bias)	High risk	Only 1 outcome measure
Other bias	Unclear risk	Vested interest bias: insufficient information No baseline imbalance; sample size calculation was not reported; the trial was not stopped early

Angelico 2004

Methods	Randomised, open-label, controlled trial in naive patients in 14 centres 12 months therapy, 6 months follow-up
Participants	**Country:** Italy 181 patients were enrolled and started the initial 2-month treatment course with interferon-alpha-2a monotherapy. 17 patients dropped out within this period. The remaining 164 patients were randomised **Inclusion criteria:** age between 18 and 65 years, presence of anti-HCV antibodies, positive serum HCV RNA by PCR, persistent elevation of serum ALT (≥ 1.5 times the upper limit of normal) during the 12 months prior to the study, and histological diagnosis of chronic hepatitis on liver biopsy sample taken in the preceding 6 months **Exclusion criteria:** HBsAg or HIV positivity, recent or active alcohol and/or drug abuse, platelet count < 70,000/mL or leucocyte count < 3000/mL, histological evidence of cirrhosis, autoimmune or genetic liver diseases, other clinically significant diseases. **Amantadine group:** 83 patients, mean age 39 ± 13 years, male/female = 61/22. Serum ALT 123 ± 73 MU/mL and the basal viral load 766 ± 747 x 10^3 copies per mL. Genotype 1 (n = 45) and genotype non-1 (n = 38). Histological staging: median 1.7 ± 1.3 **Control group:** 81 patients, mean age 41 ± 12 years, male/female = 53/28. Serum ALT 110 ± 66 MU/mL and the basal viral load 738 ± 585 x 10^3 copies per mL. Genotype 1 (n = 46) and genotype non-1 (n = 35). Histological staging: median 1.5 ± 1.1
Interventions	First there was an initial treatment course of 3 MU of recombinant interferon-alpha-2a, sc 3 times weekly for 2 months. Patients were then

	divided into 2 groups according to the serum HCV RNA status (HCV RNA-negative or HCV RNA-positive). Patients in each group were randomly assigned to receive: **Amantadine group:** interferon-alpha-2a sc 3 times weekly plus amantadine, 200 mg po daily **Control group:** interferon-alpha-2a sc 3 times weekly In the HCV RNA-positive group, the dose of interferon-alpha-2a was increased to 6 MU 3 times weekly. At the end of month 6 of treatment, HCV RNA status was re-assessed. All HCV RNA-positive patients were withdrawn from therapy, whereas HCV RNA-negative patients continued treatment until month 12 according to their initial randomization
Outcomes	Mortality; liver-related morbidity; SAE; treatment discontinuation due to AE; number of patients without SVR; number of patients with detectable HCV RNA at EOT; number of patients without normalisation of ALT at EOT and at EOFU
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not placebo-controlled
Incomplete outcome data (attrition bias) All outcomes	High risk	Too many drop-outs, not specified for what reasons and in which group: this can influence intervention effect
Selective reporting (reporting bias)	High risk	Outcome measures mentioned, but lack of other outcome measures
Other bias	Unclear risk	Vested interest bias: insufficient information No baseline imbalance; sample size calculation was reported and the trial was not stopped early

Angelico 2008

Methods	Randomised clinical trial in naive patients in 12 centres The study was designed in 2001 for 48 weeks of treatment, 24 weeks of follow-up
Participants	**Country:** Italy and Sardinia 230 patients were randomised **Inclusion criteria:** interferon-naive patients with chronic HCV, age 18 to 65 years, positive serum HCV RNA, elevated serum ALT (≥ 1.5 times the upper limit of normal in at least 2 determinations over the previous 6-month period) **Exclusion criteria:** decompensated cirrhosis (presence or a history of ascites, gastrointestinal bleeding or hepatic encephalopathy); positive serum HBsAg, HIV co-infection; neutrophil count < 1500 cells/mm^3; platelet count < 90 000

	cells/mm^3; haemoglobin levels < 12 g/dl (women) or < 13 g/dl (men); serum creatinine levels > 1.5 mg/dl; active alcohol or drug dependence; pregnancy or lactation; serological markers of autoimmunity; severe psychiatric disorders and cancer or severe pulmonary, renal or cardiac comorbidity. Cirrhotic patients were eligible only classified as Child–Pugh A **Amantadine group:** 47 patients **Control group:** 42 patients Mean baseline characteristics for the whole group of 89 patients (actually 109, because the 20 patients who dropped out during the induction period belonged to this group according to ITT). Mean age 47.3 ± 12.1 years, male/female = 63/46, BMI 25.3 ± 3.5 kg/m^2. Serum ALT was 117 ± 87 IU/l and the basal viral load was 939 ± 109 x 10^3 IU per mL. Genotype 1 and 4 (n = 87) and genotype 2 and 3 (n = 22). Histological staging (Ishak): 2.3 ± 1.4	
Interventions	Randomisation was performed after the assessment of EVR, defined as undetectable qualitative serum HCV RNA (< 50 IU/ml) after 12 weeks of induction monotherapy with peg interferon-alpha-2a (40 kDa) 180 µg/week sc Patients who did not achieve EVR were randomised in a 1:1 ratio to add either: **Amantadine group:** ribavirin, 800 mg/day, in divided doses and oral amantadine hydrochloride, 200 mg/day, for 36 additional weeks **Control group:** oral ribavirin 800 mg/day, in divided doses, for 36 additional weeks Patients who achieved EVR were randomised in a 1:1 ratio either to continue peg interferon-alpha-2a monotherapy or to add oral ribavirin, 800 mg/day, for 36 additional weeks	
Outcomes	Mortality; liver-related morbidity; number of patients without SVR; number of patients with detectable HCV RNA at EOT	
Notes	At 21 January 2012 ML sent email to angelico@med.uniroma2.it about treatment discontinuation due to SAE in each group	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation was performed centrally using computer-generated lists and was stratified by individual centres and HCV genotypes (genotypes 1/4 versus genotypes non-1/4)
Allocation concealment (selection bias)	Unclear risk	Random allocation to treatment groups
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not placebo-controlled
Incomplete outcome data (attrition bias) All outcomes	High risk	Drop-outs not described completely
Selective reporting (reporting bias)	High risk	Primary outcome was mentioned, but other reasonably expected outcomes are missing

Other bias	High risk	Vested interest bias: the study medication was provided by Roche Pharmaceuticals, Monza, Italy No baseline imbalance; sample size calculation was reported; the trial was not stopped early

Bacosi 2002

Methods	Randomised clinical trial in non-responders or relapsers 12 months therapy, 12 months follow-up	
Participants	**Country:** Italy 165 patients were screened (females n = 86; males n = 79) for 3 groups (55 patients each group) **Inclusion criteria:** detectable, circulating HCV RNA; presence of chronic active liver disease already diagnosed on the grounds of laboratory and pathologic findings **Exclusion criteria:** Child-Pugh score B or C, previous episode of gastrointestinal bleeding, disturbances of cardiac rhythm as determined by electrocardiogram and renal failure **Amantadine group:** 38 patients, mean age 67 ± 4 years, male/female = 17/21. Serum ALT 2.6 ± 1.5-fold the upper limit of normal and the basal viral load 585 ± 257 x 10^3 copies per mL. Genotype 1b was predominant (n = 32) with 4 patients with mixed genotypes. The other 6 patients had genotypes 2a (n = 3) and 2a-2c (n = 3). 1 patient cirrhosis **Control group:** 39 patients, mean age 65 ± 2 years, male/female = 21/18. Basal viral load was 637 ± 452 x 10^3 copies per mL, ALT was not provided. Genotype 1b was predominant (n = 31) associated with 1a in 3 cases; the remaining 8 patients had genotypes (2a (n=4), 2a-2c (n = 3) and 4 (n = 1). No patient with cirrhosis	
Interventions	**Amantadine group:** interferon-alpha-n_3 6 MU sc every other day until return to normal of ALT or a decrease in viral copies of at least 1 log unit (however, no longer than 3 months) then followed by 3 MU plus 200 mg/day amantadine orally **Control group:** interferon-alpha-n_3 6 MU sc every other day until return to normal of ALT or a decrease in viral copies of at least 1 log unit (however, no longer than 3 months) then followed by 3 MU Another included group received only 100 mg amantadine oral twice daily The duration of the trial treatment was 12 months; treatment, however, was planned to last for no more than 6 months if there was no significant decrease in viral load	
Outcomes	Mortality; SAE; treatment discontinue due to AE; number of patients without SVR; number of patients with detectable HCV RNA at EOT; number of patients without normalisation of ALT at EOT and at EOFU	
Notes	ML sent Dr Bacosi an email for additional information on 13 December 2011	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information

Allocation concealment (selection bias)	Low risk	Closed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not placebo-controlled
Incomplete outcome data (attrition bias) All outcomes	High risk	Drop-outs not equally divided. Many patients dropped out after randomisation
Selective reporting (reporting bias)	High risk	No clear primary and secondary outcome measures mentioned
Other bias	Unclear risk	Vested interest bias: insufficient information No baseline imbalance; sample size calculation was not reported; the trial was not stopped early

Baisini 2003

Methods	Randomised, open-label, controlled trial in naive patients involving 5 centres 12 months therapy, 6 months follow-up
Participants	**Country:** Italy 93 patients were randomised **Inclusion criteria:** elevation of serum ALT > 2 times the upper limit of normal in at least 3 occasions over 12 months and with positive HCV RNA testing, histological evidence of chronic hepatitis as judged on liver biopsy performed no longer than 6 months prior to enrolment, confirmation of HCV infection by PCR **Exclusion criteria:** age < 18 years or > 65 years, pregnancy or lack of appropriate contraceptive measures in women of child bearing age, previous treatment with antiviral or immunosuppressive drugs, current or previous drug addiction, alcoholism, positive HBsAg or HIV testing, histological evidence of cirrhosis, concomitant metabolic, autoimmune or neoplastic liver diseases, severe concomitant diseases other than liver disease, history of depression or psychiatric diseases, leukocyte count < 3000/dL, platelet count < 75,000/dL and serum albumin < 3 g/dL **Amantadine group:** 48 patients, mean age 48 ± 1.8 years, male/female = 24/24. Serum ALT 130 ± 15 U/l and 32 patients had a basal viral load > 1 x 10^6 copies per mL. Genotype 1 (n = 22). Histological staging 1.7 ± 0.3 **Control group:** 45 patients, mean age 45 ± 1.8 years, male/female = 27/18. Serum ALT 115 ± 10 U/l and 32 patients had a basal viral load > 1 x 10^6 copies per mL. Genotype 1 (n = 19). Histological staging 1.3 ± 0.2
Interventions	i) Phase 1 (week 0/4): patients received either interferon-alpha lymphoblastoid 6 MU daily plus 100 mg amantadine twice daily; or the same dose of interferon-alpha alone (regimen B) ii) Phase 2 (week 5/24): all patients in regimen A and in regimen B were shifted to receive interferon-alpha 6 MU 3 times a week while maintaining the amantadine dose as in phase 1 for patients allocated to regimen A iii) Phase 3 (week 25/48): patients with serum ALT level lower than the upper limit of the normal range at the end of phase 2 were treated with a reduced dose of interferon-alpha dose, 3 MU 3 times a week while maintaining 100

	mg twice daily amantadine for patients allocated to regimen A. Patients with abnormal ALT levels continued treatment as in phase 2	
Outcomes	Mortality; liver-related morbidity; SAE; treatment discontinuation due to AE; number of patients without SVR; number of patients without improvement of histology; number of patients without normalisation of ALT at EOTand at EOFU	
Notes	Additional information requested on 9 February 2012 from the last author Prof. Dr. A. Lanzini	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The method of sequence generation was not specified. Carried out using a blocked randomisation technique
Allocation concealment (selection bias)	Unclear risk	The method of allocation concealment was not specified. Carried out using a blocked randomisation technique
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not placebo-controlled
Incomplete outcome data (attrition bias) All outcomes	High risk	Patients who terminated prematurely were not equally divided over the 2 treatment groups
Selective reporting (reporting bias)	High risk	There was no protocol, but all the authors' study endpoints were discussed in the article. Not all reasonably expected outcomes were discussed
Other bias	Unclear risk	Vested interest bias: unclear No baseline imbalance; sample size calculation was reported; the trial was not stopped early

Berg 2003

Methods	Randomised, double-blind, placebo-controlled trial in naive patients in 8 centres Patients were studied between December 1998 and June 2001 48 weeks therapy, 24 weeks follow-up
Participants	**Country:** Germany 400 patients were enrolled **Inclusion criteria:** aged between 18 and 70 years with compensated chronic HCV infection who had not been previously treated with interferon-alpha, ribavirin, and/or amantadine, positive test for anti-HCV and HCV RNA by RT-PCR, elevated serum ALT levels for at least 6 months before initiation of treatment, and liver biopsy specimen taken in the preceding year of study entry showing chronic hepatitis **Exclusion criteria:** decompensated liver disease, other causes of liver disease, hepatitis B infection, HIV infection, autoimmune disorders, haemoglobin values < 11 g/dL, white blood cell count < 3/nL, thrombocytopenia < 70/nL, other severe concurrent diseases, concurrent use of thiazide diuretics, pregnancy, or lactation period, alcohol or drug abuse or those unwilling to practice contraception

	Amantadine group: 200 patients, mean age 41.7 ± 0.82 (18 to 70) years, male/female = 126/74. Mean weight 75.6 ± 1.0 (49 to 115) kg. Mean serum ALT 62.4 ± 4.03 (16 to 393) MU/mL and the mean basal viral load 5.99 ± 0.75 x 10^6 copies per mL. Genotype 1 (n = 126), genotype 2 (n = 20), genotype 3 (n = 48), and genotype 4 (n = 6). Histological staging: F0 (n = 23), F1 (n = 79), F2 (n = 49), F3 (n = 35), and F4 (n = 14) **Control group:** 200 patients, mean age 40.5 ± 0.79 (18 to 68) years, male/female = 127/73. Mean weight 73.7 ± 1.07 (47 to 125) kg. Mean serum ALT 62.8 ± 3.72 (16 to 369) MU/mL and the mean basal viral load 4.92 ± 0.59 x 10^6 copies per mL. Genotype 1 (n = 129), genotype 2 (n = 12), genotype 3 (n = 47), genotype 4 (n = 9), and genotype 5 (n = 1). Histological staging: F0 (n = 28), F1 (n = 69), F2 (n = 52), F3 (n = 41), and F4 (n = 10)	
Interventions	**Amantadine group:** total dose of 200 mg amantadine sulphate with interferon-alpha-2a plus 1000 to 1200 mg ribavirin per day orally adjusted according to body weight (1000 mg for weight < 75 kg and 1200 mg for weight ≥ 75 kg) for 48 weeks **Control group:** matched placebo with interferon-alpha-2a plus 1000 to 1200 mg ribavirin per day orally adjusted according to body weight (1000 mg for weight < 75 kg and 1200 mg for weight ≥ 75 kg) for 48 weeks For the first 2 weeks, 9 MU interferon-alpha daily, followed by 6 MU interferon-alpha daily for an additional 6 weeks, then 6 MU 3 times per week until week 24 and then 3 MU thrice weekly for a further 24 weeks Psychological states were measured by the German adapted and validated version of the 'Profile of Mood States' (POMS) scale, which measures 4 factor scores for depression, fatigue, vigour, and anger. Furthermore, QoL was assessed by the 'Everyday Life' questionnaire (EDLQ), a German validated questionnaire related to the SF-36 Health Survey. The EDLQ assesses the following 6 subscales: body (e.g., make demands on body, concentrate on a task); mind (e.g., cope with illness, accept oneself); everyday life (e.g., solve daily problems, perform personal hygiene); social activity (e.g., get along with family, count on partner's help); zest for life (e.g., enjoy life); and medical treatment (e.g., believe in success of treatment)	
Outcomes	Mortality; liver-related morbidity; SAE; treatment discontinuation due to AE; QoL; number of patients without SVR; number of patients with detectable HCV RNA at EOT; number of patients without normalisation of ALT at EOT and at EOFU	
Notes	Study was supported by Merz + Co, Frankfurt a. M. and Hoffman-La Roche, Grenzach, Germany	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Independent central randomisation centre using a random number generator in fixed blocks of 4
Allocation concealment (selection bias)	Low risk	Independent central randomisation centre using a random number generator in fixed blocks of 4
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Matched placebo
Blinding of outcome assessment (detection	Low risk	Matched placebo

bias) All outcomes		
Incomplete outcome data (attrition bias) All outcomes	High risk	Each drop-out not explained/mentioned separately
Selective reporting (reporting bias)	Low risk	All important outcome measures reported
Other bias	High risk	Vested interest bias: supported by Merz + Co No baseline imbalance; sample size calculation was reported; the trial was not stopped early

Brillanti 1999

Methods	Randomised clinical trial in interferon-alpha non-responders in 1 centre Patients were enrolled between May and July 1996 6 months therapy, 6 months follow-up	
Participants	**Country:** Italy 20 adult patients were randomised **Inclusion criteria:** persistent elevations of serum ALT levels for at least the previous 6 months; liver biopsy obtained within the last 3 months before starting the previous interferon-alpha course, showing histological findings compatible with chronic viral hepatitis; the presence of antibodies to HCV by ELISA and of serum HCV RNA by PCR; the absence of circulating anti-interferon-alpha antibodies; no signs or symptoms of decompensated liver disease, other serious illnesses, or co-infection with HIV; previously been treated using 3 to 5 MU of recombinant or lymphoblastoid interferon-alpha on alternate days for 6 months, but neither biochemical nor virological response had been achieved; interferon-alpha had been discontinued at least 6 months before entry into study **Exclusion criteria:** active hepatitis B virus infection, autoimmune hepatitis, alcoholic liver disease, and other possible causes chronic liver disease **Amantadine group:** 10 patients, mean age 42.8 ± 2.5 years, male/female = 7/3. Mean weight not provided. Mean serum ALT 159.8 ± 22.9 MU/mL and the mean basal viral load 5.53 ± 0.22 x 10^6 copies per mL. Genotype 1 (n = 4), genotype 2 (n = 3), and genotype 3 (n = 3). Histological staging: 5 patients cirrhosis **Control group:** 10 patients, mean age 45.5 ± 5.2 years, male/female = 8/2. Mean weight not provided. Mean serum ALT 169.5 ± 49.6 MU/mL and the mean basal viral load 5.42 ± 0.19 x 10^6 copies per mL. Genotype 1 (n = 4), genotype 2 (n = 4), and genotype 3 (n = 2). Histological staging: 4 patients cirrhosis	
Interventions	**Amantadine group:** 100 mg oral amantadine per day plus 3 MU natural human leukocyte interferon-alpha-n3 on alternate days, plus 800 mg/day (if body weight < 75 kg) or 1000 mg/day (if body weight > 75 kg) ribavirin, given orally in 2 daily doses **Control group:** 3 MU natural human leukocyte interferon-alpha-n3 on alternate days plus 800 mg/day (if body weight < 75 kg) or 1000 mg/day (if body weight > 75 kg) ribavirin, given orally in 2 daily doses	
Outcomes	Mortality; liver-related morbidity; SAE; treatment discontinuation due to AE; number of patients without SVR; number of patients with detectable HCV RNA at EOT; number of patients without normalisation of ALT at EOT and at EOFU	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Random sequence generation (selection bias)	Unclear risk	Using restricted randomisation (permuted blocks) with serial entry, 10 individuals were randomly selected out of the set of 20 and allocated to the triple therapy group, and the other 10 were allocated to the double therapy group
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not placebo-controlled
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop-outs
Selective reporting (reporting bias)	High risk	No pre-planned outcome measures mentioned
Other bias	Unclear risk	Vested interest bias: insufficient information No baseline imbalance; sample size calculation was not reported; the trial was not stopped early

Brillanti 2000

Methods	Randomised clinical trial in interferon-alpha non-responders in 1 centre Patients were enrolled starting in October 1996 12 months therapy, 6 months follow-up
Participants	**Country:** Italy 60 adult patients were randomised **Inclusion criteria:** persistent elevations of serum ALT levels for at least the previous 6 months; liver biopsy obtained within the last 3 months before starting the previous interferon-alpha course, showing histological findings compatible with chronic viral hepatitis; the presence of antibodies to HCV by ELISA and of serum HCV RNA by PCR; the absence of circulating anti-interferon-alpha antibodies; previously been treated using 3 to 6 MU of recombinant or lymphoblastoid interferon-alpha on alternate days for 4 months, but neither biochemical nor virological response had been achieved; interferon-alpha had been discontinued at least 6 months, but not more than 12 months, before entering this study **Exclusion criteria:** signs or symptoms of decompensated liver disease, co-infection with HIV, active hepatitis B virus infection, autoimmune hepatitis, alcoholic liver disease, other possible causes of chronic liver disease, other clinically significant diseases, haemoglobin concentration of < 12 g/dL in women and <13 g/dL in men, white cell count of < 3000 mm^3, and platelet count of < 100,000 mm^3 **Amantadine group:** 40 patients, median age 49 (28 to 70) years, male/female = 27/13. Weight not provided. Median serum ALT 124.5 (42 to 502) IU/L and the basal viral load 5.46 GMT (GMT = geometric mean

	titre of circulating HCV RNA as the antilog of the mean of the logarithmic transformed values of copies/mL). Genotype 1 (n = 23), genotype 2 (n = 11), genotype 3 (n = 3), and genotype 4 (n = 3). Histological staging: 10 patients cirrhosis **Control group:** 20 patients, median age 47 (32 to 70) years, male/female = 13/7. Weight not provided. Median serum ALT 133 (58 to 404) IU/L and the basal viral load 5.5 GMT. Genotype 1 (n = 11), genotype 2 (n = 6), genotype 3 (n = 2), and genotype 4 (n = 1). Histological staging: 5 patients cirrhosis
Interventions	**Amantadine group:** oral amantadine hydrochloride administered twice daily at total dose of 200 mg plus 5 MU sc interferon-alpha-2b every other day and oral ribavirin 800 mg/day (if body weight < 75 kg) or 1000 mg/day (if body weight > 75 kg) ribavirin, given orally in 2 daily doses **Control group:** 5 MU sc interferon-alpha-2b every other day and oral ribavirin 800 mg/day (if body weight < 75 kg) or 1000 mg/day (if body weight > 75 kg) ribavirin, given orally in 2 daily doses
Outcomes	Mortality; liver-related morbidity. SAE. Treatment discontinuation due to AE. Number of patients without SVR; number of patients with detectable HCV RNA at EOT; number of patients without normalisation of ALT at EOT; at EOFU
Notes	Supported partially by a Research Grant from the Italian Ministry for the University and Scientific Research

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	We used a restricted randomisation with a ratio of 2:1
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not placebo-controlled
Incomplete outcome data (attrition bias) All outcomes	Low risk	Treatment was not discontinued in any patient because of adverse events
Selective reporting (reporting bias)	Low risk	All reasonably expected study endpoints were discussed in the article
Other bias	Unclear risk	Vested interest bias: insufficient information No baseline imbalance; sample size calculation was reported; the trial was not stopped early

Calay 2005

Methods	Multicentre, randomised, double-blind, placebo-controlled trial in naive patients 48 weeks treatment, 24 weeks follow-up
Participants	**Country:** France 269 patients were randomised, 253 really started with treatment Patients with chronic HCV (proven by liver biopsy and positive for serum HCV RNA), previous treatment naive

	Baseline characteristics were comparable in both groups: **Amantadine group:** 128 patients, mean age 44.4 years, male/female = 78/50, BMI 23 kg/m^2. Mean serum ALT was 2.3 times the upper limit of normal and the basal viral load was 1.3 MUI/mL. Genotype 1 (n = 88) and genotype non-1 (n = 40). Histological staging: 24 patients had extensive fibrosis and cirrhosis **Control group:** 125 patients, mean age 45.6 years, male/female = 72/53, BMI 24 kg/m^2. Mean serum ALT was 2.5 times the upper limit of normal and the basal viral load was 1.5 MUI/mL. Genotype 1 (n = 89) and genotype non-1 (n = 36). Histological staging: 22 patients had extensive fibrosis and cirrhosis
Interventions	**Amantadine group:** peg interferon-alpha-2b 1.5 µg/kg/week sc, ribavirin 800 to 1200 mg/day orally, with amantadine 200 mg/day for 48 weeks **Control group:** peg interferon-alpha-2b 1.5 µg/kg/week sc, ribavirin 800 to 1200 mg/day orally, with placebo for 48 weeks
Outcomes	Number of patients without SVR
Notes	ML sent an email to dom-larrey@chu-montpellier.fr on 23 January 2012 about baseline characteristics

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information, although placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information, although placebo-controlled
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	High risk	Did not report on all reasonable important outcome measures
Other bias	Unclear risk	Vested interest bias: research support by Schering-Plough, Roche No baseline imbalance; sample size calculation was not reported; unknown if trial was stopped early

Caronia 2001

Methods	Randomised clinical trial in naive patients in 2 centres Between 1997 and 1998 Treatment duration 48 weeks, follow-up 24 weeks
Participants	**Country:** United Kingdom 36 patients were randomised **Inclusion criteria:** age between 18 and 70 years; liver biopsy taken within 18 months of randomisation showing chronic HCV with significant necro-

	inflammation (HAI grade > 3/18) and/or fibrosis (stage > 2/6) and ALT > 1.3 times the upper limit of normal within 6 months of randomisation **Exclusion criteria:** patients with concomitant causes of liver disease, recent history of alcohol abuse (> 28 units per week within the last 6 months) or active intravenous drug use, and biopsy proven cirrhosis **Amantadine group:** 18 patients, mean age 40 ± 12.2 years, male/female = 9/9. Serum mean ALT was 69 ± 43.9 U/L, the basal viral load was not provided. Genotype 1 (n = 9), genotype non-1 (n = 9). Histological staging was not provided, presence of cirrhosis = 0 patients **Control group:** 18 patients, mean age 42 ± 14.3 years, male/female = 9/9. Serum ALT was 74 ± 52.6 U/L, the basal viral load was not provided. Genotype 1 (n = 10), genotype non-1 (n = 8). Histological staging was not provided, presence of cirrhosis = 0 patients
Interventions	**Amantadine group:** interferon-alpha-2a 4,5 MU sc 3 times weekly and amantadine hydrochloride, 200 mg oral daily, both for 48 weeks **Control group:** interferon-alpha-2a 4,5 MU sc 3 times weekly for 48 weeks
Outcomes	Mortality; liver-related morbidity; treatment discontinuation due to AE
Notes	Additional information requested on 26 January 2012 from the last author Prof. Dr. G. Foster. Dr. Foster responded on 26January 2012. ML responded on 31 January 2012

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	High risk	Sealed envelopes. Not opaque
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not placebo-controlled
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 patient in each group withdrew because of side effects
Selective reporting (reporting bias)	High risk	Not clearly mentioned what the primary and secondary outcome measures are. All the authors' study endpoints were discussed in the article. Not all reasonably expected outcomes were discussed
Other bias	High risk	Vested interest bias: Roche No baseline imbalance; sample size calculation was not reported; the trial was not stopped early

Caronia 2001a

Methods	Randomised clinical trial in naive patients in 14 centres Between 1998 and 2000 Treatment duration 48 weeks, follow-up 24 weeks
Participants	**Country:** United Kingdom

	143 patients were randomised **Inclusion criteria:** age between 18 and 70 years; liver biopsy taken within 18 months of randomisation showing chronic hepatitis C with significant necro-inflammation (HAI grade > 3/18) and/or fibrosis (stage >2/6) and ALT > 1.3 times the upper limit of normal within 6 months of randomisation **Exclusion criteria:** patients with concomitant causes of liver disease, recent history of alcohol abuse (> 28 units per week within the last 6 months) or active intravenous drug use **Amantadine group:** 72 patients, mean age 43 ± 17.6 years, male/female = 45/27. Serum median ALT was 76 ± 10.6 U/L, the basal viral load was not provided. Genotype 1 (n = 19), genotype non-1 (n = 53). Histological staging was not provided, presence of cirrhosis = 6 or 7 patients **Control group:** 71 patients, mean age 42 ± 21.6 years, male/female = 43/37. Serum ALT was 80 ± 39 U/L, the basal viral load was not provided. Genotype 1 (n = 20), genotype non-1 (n = 51). Histological staging was not provided, presence of cirrhosis = 7 patients	
Interventions	**Amantadine group:** interferon-alpha-2a 4.5 MU sc 3 times weekly and amantadine hydrochloride, 200 mg oral daily, both for 48 weeks **Control group:** interferon-alpha-2a 4.5 MU sc 3 times weekly for 48 weeks	
Outcomes	Mortality; liver-related morbidity; treatment discontinuation due to AE	
Notes	Additional information requested on 26 January 2012 from the last author Prof. Dr. G. Foster. Dr. Foster responded 26 January 2012. ML responded on 31 January 2012	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	High risk	Sealed envelopes. Not opaque
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Independent laboratory performed all the PCR tests and all samples were provided to the laboratory in a coded, anonymous fashion
Incomplete outcome data (attrition bias) All outcomes	High risk	The exact reasons for patients who terminated prematurely were not clearly explained
Selective reporting (reporting bias)	High risk	Not clearly described what the primary and secondary outcome measures are. All the authors' study endpoints were discussed in the article. Not all reasonably expected outcomes were discussed
Other bias	High risk	Vested interest bias: Roche No baseline imbalance; sample size calculation was not reported; the trial was not stopped early

Ciancio 2006

Methods	Randomised clinical trial in non-responders Between May 2001 and December 2002 patients were included 12 months therapy, 6 months follow-up	
Participants	**Country:** Italy 161 patients were randomised **Inclusion criteria:** age > 18 and < 65 years; positive results for HCV RNA by PCR; chronic HCV at liver biopsy performed within 1 year before entry; previous non-response to combined therapy; abnormal ALT levels (at least 1.5 times upper limit of normal; range: 0 to 40 IU) **Exclusion criteria:** previous course with peg interferon-alpha-based therapy; relapse after 1 or more interferon-alpha plus ribavirin courses; positive HBsAg test in serum; positive test for antibody to HIV; alcoholic liver disease; haemochromatosis; Wilson's disease; drug related liver disease; autoimmune hepatitis; haemoglobin level < 10 g/dL, platelet count < 70,000/mm^3, white blood cell count < 3000/mm^3, or granulocyte count < 1500/mm^3; decompensated cirrhosis; intravenous drug abuse; abnormal serum uric acid level; presence of concomitant significant medical illness; history of haemolytic anaemia; a1-antitrypsin deficiency; obesity-induced liver disease; haemophilia; seizure disorders; ischaemic cardiovascular disease and severe mental depression. Pregnant women and patients unable to practice contraception during therapy and follow-up **Amantadine group:** 80 patients, mean age 50 ± 11 (22 to 65) years, male/female = 59/21, BMI 24.8 ± 3.4 (17.3 to 33) kg/m^2. Mean serum ALT was 116 ± 85 (43 to 335) IU/L, the basal viral load was 2.1 ± 3.1 (0.01 to 19) x 10^6 Eq/mL. Genotype 1 (n = 67), genotype 2 (n = 4), genotype 3 (n = 1), and genotype 4 (n = 8). Mean histological staging was 3 ± 1.5 (0 to 6), presence of cirrhosis = 11 patients **Control group:** 81 patients, mean age 50 ± 11 (27 to 65) years, male/female = 60/21, BMI 24.9 ± 3.5 (17.6 to 34.2) kg/m^2. Mean serum ALT was 127 ± 84 (39 to 770) IU/L, the basal viral load was 1.8 ± 3.1 (0.07 to 18) x 10^6 Eq/mL. Genotype 1 (n = 66), genotype 2 (n = 9), genotype 3 (n = 3), and genotype 4 (n = 3). Mean histological staging was 3 ± 1.5 (0 to 6), presence of cirrhosis = 7 patients	
Interventions	**Amantadine group:** 180 µg once weekly of peg interferon-alpha-2a plus ribavirin, either 1000 mg/day (body weight < 75 kg) or 1200 mg/day (body weight > 75 kg) plus amantadine 200 mg daily for 12 months **Control group:** 180 µg once weekly of peg interferon-alpha-2a plus ribavirin, either 1000 mg/day (body weight < 75 kg) or 1200 mg/day (body weight > 75 kg) for 12 months	
Outcomes	Mortality; liver-related morbidity; SAE; treatment discontinuation due to AE; number of patients without SVR; number of patients with detectable HCV RNA at EOT	
Notes	ML sent an email to g.saracco@tin.it on 23 January 2012 about treatment discontinuation due to AE in both groups. Dr. Saracco answered with additional information on 23 January 2012	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Each patient was allocated through a concealed process, using a computerised program with block randomisation at a central location

Allocation concealment (selection bias)	Low risk	Each patient was allocated through a concealed process, using a computerised program with block randomisation at a central location
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not placebo-controlled
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Numbers of patients withdrawn due to adverse events in text does not match with number of patients in table. Unknown if all patients who withdrew from the study were reported
Selective reporting (reporting bias)	High risk	Primary outcome mentioned, but lack of other outcome measures
Other bias	Low risk	Vested interest bias: no external funding was received for this study No baseline imbalance; sample size calculation was not reported; the trial was not stopped early

Cornberg 2000

Methods	Randomised, placebo-controlled trial in interferon non-responders 12 months therapy, 6 months follow-up	
Participants	**Country:** Germany 26 patients were randomised **Amantadine group:** 14 patients, mean age 38 years, male/female = 14/0. Serum ALT was not provided, the mean basal viral load was 1,099,643 copies per mL. Genotype 1a/b (n = 13), genotype non-1 (n = 1). Histological staging was not provided **Control group:** 89 patients, mean age 41 years, male/female = 12/0. Serum ALT was not provided, the mean basal viral load was 1,420,417 copies per mL. Genotype 1a/b (n = 9), genotype non-1 (n = 3). Histological staging was not provided	
Interventions	**Amantadine group:** interferon 2 weeks 10 MU daily, 2 weeks 5 MU daily, 8 weeks 3 MU daily followed by 3 MU every other day for further 9 months plus daily 1000 to 1200 mg ribavirin and 200 mg amantadine orally once daily **Control group:** interferon 2 weeks 10 MU daily, 2 weeks 5 MU daily, 8 weeks 3 MU daily followed by 3 MU every other day for further 9 months plus daily 1000 to 1200 mg ribavirin and placebo orally once daily	
Outcomes	Mortality; liver-related morbidity; SAE; treatment discontinuation due to AE; number of patients without SVR; number of patients with detectable HCV RNA at EOT	
Notes	ML sent Dr. Cornberg an email on 12 January 202012 about the biochemical responses. Dr Cornberg responded the same day	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information

Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information, although the study is placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information, although the study is placebo-controlled
Incomplete outcome data (attrition bias) All outcomes	Low risk	26 patients were enrolled and completed treatment
Selective reporting (reporting bias)	High risk	Only reported virological response
Other bias	Unclear risk	Insufficient information

Ferenci 2006

Methods	Randomised, double-blind, placebo-controlled study in naive patients 48 weeks therapy, 72 weeks follow-up (24 weeks follow-up also measured)
Participants	**Country:** Austria 233 patients screened and received interferon sensitivity test; 211 randomised **Inclusion criteria:** treatment-naive patients with chronic HCV, genotype 1 infection, liver biopsy findings consistent with diagnosis of chronic HCV (obtained within 6 months), and elevated serum ALT activity (> 1.5 times the upper limit of normal) in the previous 6 months and during screening; haemoglobin values ≥ 12 g/dL (women) or ≥ 13 g/dL (men), leukocytes ≥ 3000/mL and platelets ≥ 100,000/mL **Exclusion criteria:** refusal by women of child-bearing age or by sexually active patients to use effective contraception; pregnancy or breastfeeding; decompensated liver disease; coronary heart disease; co-infection with HIV or hepatitis B; overt psychiatric disorders; active alcohol or drug abuse; diabetes mellitus requiring medical therapy; autoimmune disorders and/or any other unstable medical condition not due to liver disease. Due to the potential adverse effects of amantadine, patients with Parkinson's disease, narrow angle glaucoma or adenoma of the prostate gland **Amantadine group:** 114 patients, mean age 45 ± 11 years, male/female = 68/46, mean BMI 25.5 ± 4.2 kg/m^2. Median serum ALT was 47 (18 to 313) IU/L, the median basal viral load was 0.465 (0.023 to 3.82) x 10^6 IU/mL. Genotype 1a (n = 23), genotype 1b (n = 73), and genotype 1a and 1b (n = 18). Histological staging: F0-F2 = 83; F3 = 15; F4 = 16 **Control group:** 95 patients, mean age 44 ± 10 years, male/female = 65/30, mean BMI 25.7 ± 3.9 kg/m^2. Median serum ALT was 54 (21 to 208) IU/L, the median basal viral load was 0.417 (0.0009 to 4.0) x 10^6 IU/mL. Genotype 1a (n = 27), genotype 1b (n = 43), and genotype 1a and 1b (n = 25). Histological staging: F0-F2 = 71; F3 = 10; F4 = 14
Interventions	**Amantadine group:** peg interferon-alpha-2a (40KD) 180 µg/week plus ribavirin 1000 to 1200 mg/day and oral amantadine 100 mg twice daily **Control group:** peg interferon-alpha-2a (40KD) 180 µg/week plus ribavirin 1000 to 1200 mg/day and a matched placebo. Compliance was assessed by counting unused syringes and tablets at each visit
Outcomes	Mortality; liver-related morbidity; SAE; treatment discontinuation due to AE; QoL; number of patients without SVR
Notes	—

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation was performed centrally using an adaptive biased coin design, stratified for study centre, the interferon sensitivity stratum, and fibrosis grade (Metavir 0/1/2 versus 3/4). Since this was a dynamic unrestricted procedure, the allocation sequence was produced during the study and unequal numbers of patients per treatment group were considered to be acceptable
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Matched placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Matched placebo, but insufficient information
Incomplete outcome data (attrition bias) All outcomes	High risk	No missing outcome data, but they used the last observation carried forward method
Selective reporting (reporting bias)	High risk	Outcome measures were reported, but no example histological outcomes and outcomes per treatment group (EOT in amantadine versus control group)
Other bias	High risk	Vested interest bias: high risk: This study reported an unrestricted research grant from Roche Austria, Vienna No baseline imbalance; sample size calculation was reported; the trial was not stopped early

Gaeta 2001

Methods	Randomised clinical trial in non-responders to interferon 6 months therapy, 6 months follow-up
Participants	**Country:** Italy 40 patients were randomized **Inclusion criteria:** persistent serum ALT levels of > 1.5 times the upper normal limit; presence of anti-HCV antibodies and HCV RNA in serum; histological features of chronic hepatitis in a liver biopsy obtained in the previous 12 months; HCV genotype 1b **Exclusion criteria:** age older than 60 years, decompensated cirrhosis, kidney disease, current use of antihistamine drugs, HBsAg or anti-HIV positivity and any of the major contraindications to interferon treatment **Amantadine group:** 21 patients, mean age 44.7 ± 9.2 years, male/female = 14/7. Serum median ALT was 130 U/L and the basal viral load was 1.0 x 10^6 copies per mL. Genotype 1b (n = 21). Histological staging: median 1.5; presence of cirrhosis = 1 **Control group:** 19 patients, mean age 48.4 ± 9.3 years, male/female = 12/7. Serum ALT was 134 U/L and the basal viral load was 1.2 x 10^6 copies per mL. Genotype 1b (n = 19). Histological staging: median 1.5; presence of cirrhosis = 2

Interventions	**Amantadine group:** interferon-alpha-2a 4.5 MU sc daily for 4 weeks, followed by 6 MU sc thrice weekly for an additional 5 months and amantadine sulphate 100 mg orally twice daily for the complete 6 months **Control group:** interferon-alpha-2a 4.5 MU sc daily for 4 weeks, followed by 6 MU sc thrice weekly for an additional 5 months
Outcomes	Mortality; treatment discontinuation due to AE; number of patients without SVR; number of patients with detectable HCV RNA at EOT; number of patients without normalisation of ALT at EOT and at EOFU
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated list
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not placebo-controlled
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	High risk	Not clearly stated what the primary and secondary outcome measures are
Other bias	Unclear risk	Vested interest bias: unclear No baseline imbalance; sample size calculation was not reported; the trial was not stopped early

Gramenzi 2007

Methods	Randomised, multicentre study in interferon-alpha non-responders Patients were enrolled between September 1998 and April 1999 48 weeks therapy, 24 weeks follow-up
Participants	**Country:** Italy 75 patients were randomised **Inclusion criteria:** histologically proven chronic HCV non-responders to a previous course of 3 to 6 MU recombinant interferon-alpha 3 times a week for at least 16 weeks with or without ribavirin, failure to clear HCV RNA from serum and to normalise serum ALT during treatment period, with persistent positivity of HCV RNA for at least 12 months and persistent ALT levels greater than 1.5 times the normal value **Exclusion criteria:** aged ≤ 18 and ≥ 64 years; decompensated liver disease; co-infection with HIV, HBsAg positivity; evidence of any cause of liver disease other than chronic hepatitis C; serum haemoglobin concentration of < 12 g/dL for women or < 13 g/dL for men; white cell count of < 3000/mm^3; neutrophil count of < 1500/mm^3; platelet count of < 70,000 mm^3; presence of haemoglobinopathy or haemolytic anaemia; alcohol abuse; drug abuse; pregnancy; other clinically significant diseases

	Amantadine group: 25 patients, mean age 50.1 ± 10.0 years, male/female = 15/10. Weight was not provided. Mean serum ALT 114.4 ± 69.8 U/L and mean basal viral load 2.3 ± 2.0 MEq/mL. Genotype 1 (n = 19), genotype 2 (n = 3), and genotype 3 (n = 3). Histological staging: 7 patients cirrhosis **Control group:** 24 patients, mean age 49.7 ± 11.3 years, male/female = 16/8. Weight was not provided. Mean serum ALT 120.8 ± 77.9 U/L and mean basal viral load 2.3 ± 2.9 MEq/mL. Genotype 1 (n = 18), genotype 2 (n = 3), genotype 3 (n = 2), and genotype 4 (n = 1). Histological staging: 5 patients cirrhosis	
Interventions	**Amantadine group:** oral amantadine hydrochloride administered twice daily at a total dose of 200 mg, plus 6 MU sc interferon-alpha-2a every other day for the first 4 weeks, followed by a dose of 3 MU per day for the remaining 44 weeks, and 15 mg/kg per day of oral ribavirin **Control group:** 6 MU sc interferon-alpha-2a every other day for the first 4 weeks, followed by a dose of 3 MU per day for the remaining 44 weeks and 15 mg/kg per day of oral ribavirin There was a third study group in this trial: 6 MU sc interferon-alpha-2a every other day for the first 4 weeks, followed by a dose of 3 MU per day for the remaining 44 weeks	
Outcomes	Mortality; liver-related morbidity; SAE; treatment discontinuation due to AE; number of patients without SVR; number of patients with detectable HCV RNA at EOT; number of patients without normalisation of ALT at EOT and at EOFU	
Notes	—	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Patients were randomly assigned to one of 3 different treatment groups
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not placebo-controlled
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Drop-outs mentioned, but not divided by groups
Selective reporting (reporting bias)	High risk	Only 1 study endpoint
Other bias	Unclear risk	Vested interest bias: insufficient information No baseline imbalance; sample size calculation was reported; the trial was not stopped early

Hasan 2004

Methods	Randomised clinical trial in non-responders The study was conducted between March 2000 and February 2002 48 weeks therapy, 24 weeks follow-up
Participants	**Country:** Kuwait

	63 patients were randomised **Inclusion criteria:** age between 18 and 65 years; HCV RNA detectable in serum at concentrations > 3200 copies/mL (615 IU/mL) by a branched DNA assay within 3 months of enrolment; prior treatment for at least 6 months with a combination of unmodified interferon-alpha-2a or alpha-2b plus ribavirin; persistence of HCV RNA in serum at the end of combination therapy (non-responder); and evidence of chronic hepatitis with or without cirrhosis **Exclusion criteria:** transient virological response during or at the end of combination therapy, followed by a relapse; clinical or biochemical evidence of hepatic decompensation; suspicion of hepatocellular carcinoma; white blood cell count < 2.5×10^9/l, haemoglobin < 110 g/l, platelet count < 60×10^9/l; serum creatinine > 140 µmol/l; alcohol or drug abuse; and severe comorbid medical or psychiatric conditions **Amantadine group:** 42 patients, median age 42 (17 to 56) years, male/female = 34/8, BMI not provided. Median serum ALT 90 (62 to 184) IU/L, median basal viral load 2.1 (0.3 to 15) x 10^6 eq/mL. Genotype 1a/1b (n = 8), genotype 4 (n = 33), and genotype 1 (n = 1). Histological staging: F1/F2 = 22; F3/F4 = 20 **Control group:** 21 patients, median age 43 (20 to 61) years, male/female = 16/5, BMI not provided. Median serum ALT 96 (60 to 201) IU/L, median basal viral load 2.3 (0.6 to 17) x 10^6 eq/mL. Genotype 1a/1b (n = 4), genotype 4 (n = 17). Histological staging: F1/F2 = 12; F3/F4 = 9
Interventions	Patients were randomised in a 2:1 ratio: **Amantadine group:** peg interferon-alpha-2b sc once weekly, at a dose of 1.5 µg/kg, ribavirin orally at a dose of 1000 mg or 1200 mg per day for patients weighing < 75 kg and ≥ 75 kg, and amantadine 200 mg/day **Control group:** peg interferon-alpha-2b sc once weekly, at a dose of 1.5 µg/kg, ribavirin orally at a dose of 1000 mg or 1200 mg per day for patients weighing < 75 kg and ≥ 75 kg
Outcomes	Mortality; liver-related morbidity; SAE; treatment discontinuation due to AE; number of patients without SVR; number of patients with detectable HCV RNA at EOT; number of patients without normalisation of ALT at EOT and at EOFU
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomly assigned, insufficient information
Allocation concealment (selection bias)	Unclear risk	Randomly assigned, insufficient information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not placebo-controlled
Incomplete outcome data	Unclear risk	Insufficient information. The number of patients who completed the entire scheduled dose was reported, but information about

(attrition bias) All outcomes		withdrawals was missing, only 3 patients withdrew because of side effects, so it is not clear what happened to the other 2.
Selective reporting (reporting bias)	Low risk	Reported on all important outcomes
Other bias	Unclear risk	Vested interest bias unclear No baseline imbalance; sample size calculation was reported; the trial was not stopped early

Helbling 2002

Methods	Double-blind, randomised, placebo-controlled trial in naive patients, in 28 centres 12 months therapy, 24 weeks follow-up	
Participants	**Country:** Switzerland 254 patients were enrolled, 8 patients withdrew informed consent after baseline evaluation, but before starting treatment. 246 started treatment **Inclusion criteria:** patients aged 18 to 65 years with biopsy-proven (within ≤ 2 years) chronic HCV who had never been treated before, exhibited elevated ALT within 6 months of entry on at least 2 occasions at least 1 month apart, and tested positive for HCV RNA in serum by RT-PCR **Exclusion criteria:** any other cause of liver disease including HBV co-infection, and alcohol intake > 20 g/day in females and > 40 g/day in males; history of or actual decompensation of liver disease; cirrhosis ≥ 8 Child-Pugh points; leucocytes < 2000/µL, neutrophils < 50,000/µL, serum creatinine > 1.5 times upper limit of normal **Amantadine group:** 121 patients, age 39 (20 to 66) years, male/female = 68/53. Serum ALT 101 U/L (34 to 421) and basal viral load 2.16 x 10^6 copies per mL. Genotype 1 (n = 62), genotype 2 (n = 12), genotype 3 (n = 34), genotype 4 (n = 5), and genotype 6 (n = 1). The other 6 patients had genotypes 2a (n = 3) and 2a-2c (n = 3). Histological staging: mild = 59, moderate = 43, severe = 18 **Control group:** 125 patients, age 38 (20 to 65) years, male/female = 70/55. Serum ALT 111 U/L (30 to 768) and basal viral load 4.72 x 10^6 copies per mL. Genotype 1 (n = 52), genotype 2 (n = 11), genotype 3 (n = 50), and genotype 4 (n = 6). Histological staging: mild = 29, moderate = 91, severe = 4	
Interventions	**Amantadine group:** interferon-alpha-2a 6 MIU sc thrice weekly for 20 weeks, followed by 3 MIU sc thrice weekly for an additional 32 weeks and amantadine sulphate 100 mg oral twice daily **Control group:** interferon-alpha-2a 6 MIU sc thrice weekly for 20 weeks, followed by 3 MIU sc thrice weekly for an additional 32 weeks and placebo oral twice daily Treatment was stopped if after 10 weeks HCV RNA in serum remained detectable by RT-PCR	
Outcomes	Mortality; SAE; treatment discontinuation due to AE; QoL. Number of patients without SVR; number of patients with detectable HCV RNA at EOT; number of patients without normalisation of ALT at EOT and at EOFU	
Notes	ML sent an email to Prof Dr. Renner on 23 December 2011 about the drop-out rate. ML forwarded this email on 9 January 2012 to Dr. Helbling	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Random sequence generation (selection bias)	Low risk	Randomisation was carried out in blocks of 10 using random numbers stratified according to the presence/absence of cirrhosis
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Matched placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	HCV RNA was determined centrally. A single pathologist (CG), unaware of clinical data including treatment response, scored all pretreatment liver biopsies using the extended Knodell score
Incomplete outcome data (attrition bias) All outcomes	High risk	Numbers of patients who withdrew due to adverse events in text do not match the numbers of patients in the table. Unknown if all patients who withdrew from the study were reported
Selective reporting (reporting bias)	High risk	All the authors' study endpoints were discussed in the article. Not all reasonably expected outcomes were discussed
Other bias	High risk	Vested interest bias: Roche No baseline imbalance; sample size calculation was reported; the trial was not stopped early

Herrine 2005

Methods	Randomised, controlled, multicentre trial in relapsers or patients who had a viral breakthrough 48 weeks therapy, 24 weeks follow-up
Participants	**Country:** United States of America 124 patients were randomised, 123 received at least 1 dose of study medication **Inclusion criteria:** adult patients with serologic evidence of HCV infection, by a positive anti-HCV antibody test and detectable HCV RNA in serum, who had a virologic response during treatment with standard interferon-alpha-2b plus ribavirin and had relapsed after at least 24 weeks of treatment or had a virologic breakthrough while still on treatment; serum ALT activity above the upper limit of normal during the 6 months before entering the study; liver biopsy consistent with chronic HCV infection in the previous 36 months; and a minimum of 24 weeks since cessation of standard interferon-alpha-2b plus ribavirin treatment, with no interferon therapy during this time **Exclusion criteria:** had received any systemic antiviral therapy within 24 weeks of the start of the study or were expected to need any systemic antiviral therapy during the study or had acute hepatitis A or B infection, HIV infection, decompensated liver disease, neutropenia (< 1500 neutrophils/mm^3), anaemia (haemoglobin < 12 g/dL in women and < 13 g/dL in men), thrombocytopenia (platelets, < 90,000/mm3), serum creatinine level higher than 1.5 times the upper limit of normal, history of alcohol or drug abuse within 1 year of entry, history of severe psychiatric disease, serum α-fetoprotein level > 100 ng/mL, or substantial coexisting medical conditions **Amantadine group:** 31 patients, mean age 46 years, male/female = 20/11, BMI not provided. Mean serum ALT 67 SE 9 U/L, mean AST 45 SE 6

	U/L, basal viral load ≤ 800,000 IU/mL: 12, and > 800,000IU/mL: 19. Genotype 1 (n = 25) and genotype non-1 (n = 6). Histological staging: non-cirrhosis = 27; cirrhosis = 4 **Control group:** 32 patients, mean age 48 years, male/female = 24/8, BMI not provided. Mean serum ALT 75 SE 10 U/L, mean AST 60 SE 7 U/L, basal viral load ≤ 800,000 IU/mL: 14, and > 800,000IU/mL: 18. Genotype 1 (n = 25) and genotype non-1 (n = 7). Histological staging: non-cirrhosis = 23; cirrhosis = 9	
Interventions	Patients were randomly assigned at a 1:1:1:1 ratio to: **Amantadine group:** sc weekly injections of 180 µg peg interferon-alpha-2a plus orally administered ribavirin, 800 mg/day in split doses for patients weighing < 75 kg and 1000 mg/day in split doses for those weighing ≥ 75 kg, and amantadine 200 mg/day for 48 weeks **Control group:** sc weekly injections of 180 µg peg interferon-alpha-2a plus orally administered ribavirin for 48 weeks in the same dosage as mentioned at the amantadine group 2 other intervention groups were: peg interferon-alpha-2a plus mycophenolate mofetil and peg interferon-alpha-2a plus amantadine, both also for 48 weeks in the same dosages as mentioned above, with a daily dose of mycophenolate mofetil of 1 g twice daily Randomisation was stratified according to HCV genotype (type 1 versus non-type 1, with any patient positive for both type 1 and non-type 1 categorised as type 1), viral load (≤ 800,000 or > 800,000 IU/mL), and relapse versus breakthrough	
Outcomes	Mortality; liver-related morbidity; SAE; treatment discontinuation due to AE; number of patients without SVR; number of patients with detectable HCV RNA at EOT; number of patients without normalisation of ALT at EOFU	
Notes	—	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not placebo-controlled
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information. Withdrawals mentioned, but not the reason for withdrawal in all patients
Selective reporting (reporting bias)	High risk	Not every outcome we would suggest was reported on
Other bias	High risk	Vested interest bias: high: research grant from Roche No baseline imbalance; sample size calculation was reported; the trial was not stopped early

Jorge 2001

Methods	Randomised clinical trial in naive patients 12 months therapy, 24 weeks follow-up	
Participants	**Country:** Argentina 91 patients were randomized **Amantadine group:** 47 patients **Control group:** 44 patients Genotype 1 (63%), viral load, ALT, and necro-inflammatory/fibrosis scores level were similar in both groups	
Interventions	**Amantadine group:** amantadine 200 mg daily and interferon-alpha-2a 6 MU daily for 4 weeks, 3 MU daily for 8 weeks, and 3 MU 3 times a week for 12 months **Control group:** interferon-alpha-2a 6 MU daily for 4 weeks, 3 MU daily for 8 weeks, and 3 MU 3 times a week for 12 months Treatment was discontinued in patients with detectable serum HCV RNA after treatment week 24	
Outcomes	Number of patients without SVR	
Notes	ML sent an email to Dr. Daruich on 12 January 2012 about virological EOT and biochemical responses	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomly allocated, but method not described
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not placebo-controlled
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Langlet 2009

Methods	Multicentre, randomised clinical trial with parallel-group design in naive and relapsing patients Trial duration: 24 or 48 weeks, follow-up 24 weeks
Participants	**Country:** Belgium, 37 centres Number of patients randomised: 630 (actually 643, but 13 never took any study medication) **Amantadine group:** mean age 43.74 ± 12.41 years, male/female: 189/127 **Control group:** mean age 45.48 ± 12.19 years, male/female: 173/141 **Inclusion criteria:** male and female patients ≥ 18 years of age; serological evidence of chronic HCV (anti-HCV antibody test), quantifiable serum HCV

	RNA of ≥ 600 IU/mL; elevated serum ALT activity documented on at least 2 occasions within the 6 months before randomisation; histological liver alterations consistent with chronic HCV; in case of cirrhosis, a compensated liver disease (Child-Pugh Grade A) **Exclusion criteria:** non-responders to a previous therapy or had a relapse during a previous therapy (breakthrough) or after completion of any previous treatment other than interferon plus ribavirin; previous treatment with any systemic antiviral, anti-neoplastic, or immunomodulatory treatment within 6 months prior to the first dose of the study drug; chronic liver disease other than HCV; other clinically significant medical history or current disease; positive serology for HAV IgM, haemoglobin < 11 g/dL, neutrophil count < 1500 cells/mm^3, platelet count < 90,000 cells//mm^3, and serum creatinine level > 1.5 times the upper limit of normal; pregnancy
Interventions	**Amantadine group:** peg interferon-alpha, ribavirin, and amantadine, n = 316 **Control group:** peg interferon-alpha and ribavirin, n = 314 Peg-INF was given sc at a dose of 180 µg in 0.5 mL, ribavirin was given twice daily at a total oral dose of 800 to 1200 mg daily according to body weight, amantadine was given orally 100 mg twice daily Treatment was given for 24 or 48 weeks according to genotype
Outcomes	Sustained virological response; sustained biochemical response rate; early virological response rate; end of treatment virological response rate; mean reduction in HCV RNA
Notes	Additional information requested on 23 January 2012 from the last author, Prof. Dr. F. Nevens

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation included a minimisation programme by study centre
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not placebo-controlled
Incomplete outcome data (attrition bias) All outcomes	High risk	Not equally matched drop-outs and insufficient information about reasons for drop-outs
Selective reporting (reporting bias)	High risk	All outcome measures reported, but lacking some important outcome measures such as EOT ALT
Other bias	High risk	Vested interest bias: high: Roche funded No baseline imbalance; sample size calculation was reported; the trial was not stopped early

Mangia 2001

Methods	Randomised clinical trial in naive patients Patients were recruited between June and December 1998

	12 months therapy, 6 months follow-up	
Participants	**Country:** Italy 200 patients were randomised **Inclusion criteria:** raised ALT for at least 6 months, HCV RNA positive by PCR, liver biopsy performed within the previous 6 months before entry, consistent with chronic HCV **Exclusion criteria:** decompensated cirrhosis, psychiatric conditions, diabetes, autoimmune diseases, concurrent hepatitis B or HIV infections, high alcohol intake, current intravenous drug use, previous treatment with interferon, pregnancy, or concomitant significant medical illness **Amantadine group:** 99 patients, age 46 (19-67) year, male/female = 61/28. Serum ALT was not provided and basal viral load was 60 (0.3 to 400) x 10^6 copies per mL. Genotype 1 (n = 52), genotype 2a (n = 34), genotype 3 (n = 7), genotype 4 (n = 6). Histological staging: 0/1 = 63, 2/3 = 36 **Control group:** 101 patients, mean age 48 (21 to 69) year, male/female = 71/30. Serum ALT was not provided and basal viral load was 58 (1.9 to 500) x 10^6 copies per mL. Genotype 1 (n = 60), genotype 2a (n = 26), genotype 3 (n = 11), genotype 4 (n = 4). Histological staging: 0/1 = 52, 2/3 = 49	
Interventions	**Amantadine group:** interferon-alpha-2a 6 MU sc thrice weekly plus amantadine 100 mg twice daily orally for 12 months **Control group:** interferon-alpha-2a 6 MU sc thrice weekly for 12 months	
Outcomes	Mortality; liver-related morbidity; SAE; treatment discontinuation due to AE; number of patients without SVR; number of patients with detectable HCV RNA at EOT; number of patients without normalisation of ALT at EOT and at EOFU	
Notes	—	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation was performed according to centre, in blocks of 10 patients; insufficient information on sequence generation
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not placebo-controlled. A single pathologist who was unaware of the patients' treatment and response to therapy scored the pre-therapy liver biopsies for hepatic inflammation and fibrosis, according to Scheuer system
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up information was available for all patients, including those who did not complete the 12-month course of therapy
Selective reporting (reporting bias)	High risk	All the authors' study endpoints were discussed in the article. Not all reasonable outcomes were discussed
Other bias	Low risk	Invested interest bias: commercial kits for quantitative HCV RNA measurements by Roche. No further funding by manufacturers of interferon or amantadine No baseline imbalance; sample size calculation was not reported; the trial was not stopped early

Maynard 2006

Methods	Multicentre, randomised double-blind, placebo-controlled trial in non-responders Trial duration: 48 weeks, follow-up 24 weeks Enrolment began in October 2000 and the trial completed in May 2003	
Participants	**Country:** France, 23 centres Number of patients randomised: 200 (actually 202, but 2 patients from the control group did not receive any medication) **Amantadine group:** mean age 47.1 (27 to 66) years, male/female: 74/27 **Control group:** mean age 46.8 (23 to 66) years, male/female: 74/26 **Inclusion criteria:** failed to respond to a single previous 24-week cycle of interferon/ribavirin combination therapy (at least 3 MIU interferon-alpha 3 times weekly and ribavirin at a minimum dose of 600 mg/day) (non-response was defined as persistent HCV RNA in the serum during the last month of treatment); elevated serum ALT; detectable HCV RNA; neutrophil count ≥ 1000/mm^3, platelet count ≥ 100 giga/L, haemoglobin ≥ 10 g/dL; post-treatment liver biopsy within a year had to show a METAVIR histological score ≥ A1F1 and < F4 **Exclusion criteria:** co-infection with HBV or HIV; any other cause of liver disease; active drug abuse or alcohol consumption > 40 g/day; other clinically significant history or current diseases; previous amantadine use, systemic immunosuppressive or antiviral treatment during the last 24 weeks, and those with a history of interferon and/or ribavirin intolerance	
Interventions	**Amantadine group:** peg interferon-alpha-2b at a dose of 1.5 mg/kg per week sc plus oral ribavirin 800 to 1200 mg/day and oral amantadine hydrochloride 2 x 100 mg/day for 48 weeks, n = 101 **Control group:** the same dose of peg interferon-alpha-2b and ribavirin plus a placebo, n = 99 For both groups, the dose of ribavirin was adjusted according to body weight (800 mg up to 65 kg weight, 1000 mg between 65 and 85 kg, and 1200 mg for weight of 85 kg or more). All drugs were started and stopped at the same time. Treatment was administered for 48 weeks regardless of the virological response during therapy. At the end of this treatment period, patients underwent a liver biopsy and were followed up for 24 weeks	
Outcomes	Sustained virological response; biochemical response at week 72 (ALT normalisation); histological benefit; tolerance - virological and biochemical responses during therapy at weeks 12, 24, and 48	
Notes	Additional information requested on 23 January 2012 from the last author Prof. Dr. C. Trepo	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation was done using a random permuted blocks method
Allocation concealment (selection bias)	Low risk	The randomisation process was generated by the Department of Biostatistics, Hospices Civils de Lyon, Lyon, France
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information, although placebo-controlled

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information, although placebo-controlled
Incomplete outcome data (attrition bias) All outcomes	High risk	Withdrawals were reported, but not all the reasons for withdrawal
Selective reporting (reporting bias)	Low risk	All outcome measures were reported
Other bias	High risk	Vested interest bias: high: supported by Schering-Plough No baseline imbalance; sample size calculation was reported; the trial was not stopped early

Mendez-Navarro 2010

Methods	Randomised, double-blind, placebo-controlled trial in naive patients Trial duration: 48 weeks, follow-up 24 weeks Randomisation between March 2003 and June 2005
Participants	**Country:** Mexico, 1 centre Number of patients randomised: 124 **Amantadine group:** mean age 44 ± 12.29 years, male/female: 29/32 **Control group:** mean age 46.2 ± 9.82 years, male/female: 26/37 **Inclusion criteria:** men and women age 18 to 65 years with genotype 1 HCV infection defined by the presence of an HCV antibody, HCV RNA positive by RT-PCR, and genotype 1 infection; elevated serum ALT levels (40 IU/l) for at least 6 months; patients with cirrhosis were included only if they were Child-Pugh Class A (compensated disease); of Latino ethnicity (self identified as "Latino or Hispanic") with Spanish as their primary language and were born in the Mexican Republic; not previously been treated with interferon, peg interferon-alpha, ribavirin, and/or amantadine; pre-treatment liver biopsy was encouraged but not required **Exclusion criteria:** other causes of liver disease; HIV infection, hepatitis B infection; complication of portal hypertension (variceal bleeding, ascites, encephalopathy, Child-Pugh B or C, hepatocellular carcinoma); haemoglobin < 12 g/dl, platelets < 70,000 plt/mm^3; pregnancy; other clinically significant diseases; alcohol or drug abuse; refusal to use contraception during treatment
Interventions	Patients were randomly assigned to receive: **Amantadine group:** peg interferon-alpha-2a 180 µg/week plus 1000 to 1200 mg/day ribavirin according to body weight (1000 mg if < 75 kg or 1200 mg if ≥ 75 kg) plus amantadine 200 mg orally daily (amantadine hydrochloride 100 mg tablets) for 48 weeks, n = 61 **Control group:** the same regimen of peg interferon-alpha-2a plus ribavirin for 48 weeks, n = 63
Outcomes	Sustained virological response; early virological response; end of treatment response
Notes	Additional information requested on 23 January 2012 from the first author, Dr. J. Mendez-Navarro. Dr. Mendez-Navarro responded on 26 January 2012. More information was requested on 26 January, and Dr. Mendez responded the same day

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Random sequence generation (selection bias)	Low risk	The randomisation was 1:1 in a balanced design and the method for random sequence generation was a computer-based random number system
Allocation concealment (selection bias)	Low risk	Central telephone allocation for concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not placebo-controlled
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals reported; no large differences in withdrawals between the 2 groups
Selective reporting (reporting bias)	High risk	Outcome measures as described in the methods are reported, but some important outcome measures, for example biochemical response, are missing
Other bias	High risk	Vested interest bias: Chung has received a research grant from Roche No baseline imbalance; sample size calculation was not reported; the trial was not stopped early

Pessoa 2012

Methods	Randomised, controlled, multicentre trial in non-responders and relapsers Trial duration: 48 weeks, follow-up 24 weeks First patient enrolled in June 2003 and last patient completed follow-up in November 2005
Participants	**Country:** Brazil Number of patients randomised: 186 (106 non-responders and 80 relapsers); 182 actually received treatment The population was predominantly male, of white race, with a mean age of ± 50 years and a baseline HCV RNA level ≥ 800,00 IU/mL **Inclusion criteria:** adults with a positive anti-HCV antibody test, detectable HCV RNA in serum; elevated ALT serum levels on at least 2 occasions during the previous 6 months; liver biopsy result within the previous 35 months consistent with the diagnosis of chronic HCV; at least 24 weeks of previous treatment with interferon-alpha plus ribavirin of which the outcome was either virological non-response or virological relapse; previous course completed at least 12 weeks prior to enrolment **Exclusion criteria:** co-infection with hepatitis A or B or HIV; neutrophil count < 1500 cells/mm^3, serum creatinine level > 1.5 times the upper limit of normal, or haemoglobin level < 12 g/dL (women) or < 13 g/dL (men); serious chronic diseases including severe psychiatric disease or alcohol or drug abuse within 1 year; pregnant or breastfeeding women and male partners of pregnant women
Interventions	**Amantadine group:** peg interferon sc 180 µg/week plus oral ribavirin 1000 mg/day (body weight ≤ 75 kg) or 1200 mg/day (body weight > 75 kg) plus oral amantadine 200 mg/day for 48 weeks, n = 94 (n = 92 actually received at least 1 dose of treatment)

	Control group: peg interferon sc 180 µg/week plus oral ribavirin 1000 mg/day (body weight ≤ 75 kg) or 1200 mg/day (body weight > 75 kg), n = 92 (n = 90 actually received at least 1 dose of treatment)	
Outcomes	Sustained virological response; sustained biochemical response; early virological response; complete early virological response; safety: adverse events and laboratory abnormalities	
Notes	Additional information requested on 25 January 2012 from second author, Prof. Dr. H. Cheinquer. Dr. Cheinquer responded on 25 January with information about drop-outs due to AE and information on random sequence generation and allocation concealment	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation was provided by a computerised system hosted by the study contract research organisation
Allocation concealment (selection bias)	Low risk	Delivered by phone to the site
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not placebo-controlled
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups
Selective reporting (reporting bias)	High risk	All the outcomes mentioned in methods are reported, but information on biochemical EOT response is lacking
Other bias	High risk	Vested interest bias: high: Roche funding No baseline imbalance; sample size calculation was reported; the trial was not stopped early

Piai 2003

Methods	Randomised clinical trial in relapsers in 1 referral hepatologic centre Patients were enrolled between January 1999 and May 2000 and were followed up until November 2001 12 months therapy, 6 months follow-up
Participants	**Country:** Italy 49 patients entered the first period of the study **Inclusion criteria:** previously received 1 or more course of recombinant or lymphoblastoid interferon at a dose ranging from 3 to 6 MU 3 times per week for 6 to 12 months and who had normalised serum ALT and cleared serum HCV RNA by PCR on therapy but subsequently relapsed within 6 months after stopping treatment; age between 18 and 65 years; time between last course of interferon and the start of combination therapy < 12 months, liver biopsy before enrolment < 24 months; HCV genotype 1b **Exclusion criteria:** decompensated liver disease; HIV and HBV co-infection; other clinically significant diseases; haemoglobin < 13 g/dl for males and < 12 g/dl for females; platelet count < 100,000 and WBC < 3000

	Amantadine group: 12 patients, mean age 51.2 ± 4.4 years, male/female = 11/1. Mean BMI 27.5 ± 1.8 kg/m^2. Mean serum ALT 195 ± 108 IU/L and basal viral load > 1 million n = 4. Genotype 1b (n = 12). Histological staging: mean fibrosis score 2.4 ± 1.2 **Control group:** 12 patients, mean age 49.3 ± 10.0 years, male/female = 9/3. Mean BMI 26.7 ± 2.7 kg/m^2. Mean serum ALT 184 ± 115 IU/L and basal viral load > 1 million n = 4. Genotype 1b (n = 12). Histological staging: mean fibrosis score 1.9 ± 1.1
Interventions	In the first part of the study, all 49 relapsers were treated for 6 months with recombinant interferon-alpha-2b, administered sc at a dose of 3 MU thrice a week, together with ribavirin, given orally twice a day, at a total dosage adjusted according to body weight (1000 mg for patients weighing ≤ 75 kg and 1200 mg for those > 75 kg). During the second part of the study, 24 patients who showed no biochemical and virological response, were randomised to continue treatment for further 6 months in 2 arms: **Amantadine group:** interferon-alpha-2b plus ribavirin in the above mentioned dosages, plus oral amantadine hydrochloride 200 mg daily **Control group:** interferon-alpha-2b plus ribavirin in the above mentioned dosages
Outcomes	Mortality; liver-related morbidity; SAE; treatment discontinuation due to AE; number of patients without SVR; number of patients with detectable HCV RNA at EOT; number of patients without normalisation of ALT at EOT
Notes	On 9 January 2012 ML sent G. Piai an email about the number of patients in both groups with normal ALT 6 months after cessation of therapy

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes; unknown if they were opaque
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not placebo-controlled, not mentioned in article
Incomplete outcome data (attrition bias) All outcomes	Low risk	All non-responders completed the second part of therapy
Selective reporting (reporting bias)	High risk	All the authors' study endpoints were discussed in the article. Not all reasonable outcomes were discussed
Other bias	Unclear risk	The study appears to be free of other sources of bias, but insufficient information Baseline imbalance unknown; sample size calculation was reported; the trial was not stopped early

Salmeron 2007

Methods	Randomised, parallel-group trial in interferon non-responder patients in 36 centres Patients were recruited between 1999 and 2001 and the follow-up finished in March 2003

	48 weeks therapy, 24 weeks follow-up
Participants	**Country:** Spain 378 patients were randomized **Inclusion criteria:** serum HCV RNA positivity by PCR before the beginning of the treatment and serum ALT activity above the upper limit of normal with at least 1 value during the 6-month period preceding the initiation of test drug dosing. All patients had chronic hepatitis without cirrhosis in the biopsy. The biopsies had been carried out up to a maximum of 3 years before entering the study. A treatment-free interval of at least 6 months was necessary between the first and the second course **Exclusion criteria:** age 60 years or older, evidence of any cause of liver disease other than chronic HCV (co-infection with hepatitis B virus or HIV, concomitant autoimmune disease or metabolic disease). Clinically significant cardiovascular, renal, haematological, rheumatological, neurological or psychiatric disease, systemic infections, neoplastic disease, organ grafts and systemic immunosuppressive treatment. Active alcohol (alcohol intake > 40 g/day in females and > 60 g/day in males) or drug abuse within the previous year. Pregnancy or lactation period. Haemoglobin levels < 12 g/dL, white cell count < 3000/mm^3, granulocyte count < 1500/mm^3 or platelet count < 100,000/mm^3 **Amantadine group + interferon:** 111 patients, mean age 44.7 ± 9 years, male/female = 87/24. Mean weight 78 ± 13 kg. Mean serum ALT 133 ± 90 UI/L, mean serum AST 94 ± 81 UI/L, and high serum HCV RNA titre > 8 x 10^5 UI/mL was detected in 34 out of 78 patients. Genotype 1: 72 out of 88, genotype non-1: 16 out of 88. Histological staging was not provided **Control group (interferon):** 53 patients, mean age 45 ± 8 years, male/female = 40/13. Mean weight 74 ± 11 kg. Mean serum ALT 135 ± 89 UI/L, mean serum AST 103 ± 88 UI/L, and high serum HCV RNA titre > 8 x 10^5 UI/mL was detected in 12 out of 43 patients. Genotype 1: 40 out of 44, genotype non-1: 4 out of 44. Histological staging was not provided **Amantadine group + interferon + ribavirin:** 108 patients, mean age 45.3 ± 8 years, male/female = 87/21. Mean weight 78 ± 13 kg. Mean serum ALT 125 ± 80 UI/L, mean serum AST 97 ± 76 UI/L, and high serum HCV RNA titre > 8 x 10^5 UI/mL detected in 27 out of 80 patients. Genotype 1: 74 out of 82, genotype non-1: 8 out of 82. Histological staging was not provided **Control group (interferon + ribavirin):** 106 patients, mean age 46 ± 9 years, male/female = 85/21. Mean weight 77 ± 13 kg. Mean serum ALT 124 ± 92 UI/L, mean serum AST 79 ± 75 UI/L, and high serum HCV RNA titre > 8 x 10^5 UI/mL was detected in 29 out of 81 patients. Genotype 1: 74 out of 85, genotype non-1: 11 out of 85. Histological staging was not provided
Interventions	**Amantadine group + interferon:** interferon-alpha-2a, 9 MUI/day sc for 4 weeks and 3 MUI 3 times a week for a further 44 weeks plus amantadine chloride, 100 mg twice per day **Control group (interferon):** interferon-alpha-2a, 9 MUI/day sc for 4 weeks and 3 MUI 3 times a week for a further 44 weeks **Amantadine group + interferon + ribavirin:** the same doses of interferon-alpha-2a plus amantadine 100 mg twice per day, and ribavirin 1000 to 1200 mg per day according to weight

	Control group (interferon + ribavirin): the same doses of interferon-alpha-2a and ribavirin	
Outcomes	Mortality; liver-related morbidity; SAE; treatment discontinuation due to AE; number of patients without SVR; number of patients with detectable HCV RNA at EOT	
Notes	ML sent an email to Dr. Salmeron about the ALT values at EOT and at 6 months follow-up on 10 January 2012	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Patients were selected randomly by central telephone
Allocation concealment (selection bias)	Low risk	Patients were selected randomly by central telephone
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not placebo-controlled
Incomplete outcome data (attrition bias) All outcomes	High risk	All drop-outs were discussed, but not equally divided over groups
Selective reporting (reporting bias)	High risk	Not all of the study's prespecified primary outcomes have been reported. The biochemical response (normalisation of serum ALT) was not reported
Other bias	High risk	Vested interest bias: Roche No baseline imbalance; sample size calculation was reported; the trial was stopped early at 378 patients randomised (instead of 1100 patients calculated) due to poor results

Sax 2001

Methods	Randomised clinical trial in patients co-infected with HIV Patients were recruited at 2 university outpatient clinics and were enrolled within a 4-month period Trial duration: 12 months, follow-up 6 months
Participants	**Country:** Switzerland 7 patients were randomised: 3 female; mean age 40 years, range 28 to 54 years **Inclusion criteria:** patient's triple antiretroviral treatment was unchanged for at least 2 months; > 200 CD4+ lymphocytes/l; < 50,000 HIV-1 RNA copies/mL; elevated transaminases for at least 6 months; biopsy results were compatible with HCV infection **Exclusion criteria:** decompensated liver cirrhosis; additional liver diseases; ongoing illicit drug use; contraindications for interferon
Interventions	**Amantadine group:** interferon-alpha, 6 MU/day for 1 month and 6 MU thrice weekly for the remaining 11 months combined with amantadine sulphate 100 mg bid orally, n = 3 **Control group:** interferon-alpha, 6 MU/day for 1 month and 6 MU thrice weekly for the remaining 11 months alone, n = 4

Outcomes	Mortality; number of patients without SVR	
Notes	The trial stopped early due to important toxicities and low tolerability of interferon-alpha	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not placebo-controlled
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	High risk	Endpoint not clearly stated. Not all reasonably expected outcomes were discussed
Other bias	Low risk	No vested interest bias (low risk of bias regarding vested interest) Baseline imbalance unknown; sample size calculation was not reported; the trial was not stopped early

Shakil 2000

Methods	Randomised clinical trial in naive patients Trial duration: 24 weeks of therapy, 24 weeks follow-up
Participants	**Country:** United States of America 24 patients were randomised **Inclusion criteria:** ≥ 18 years, elevated serum ALT levels, positive anti-HCV and HCV RNA in serum, and chronic hepatitis on liver biopsy **Exclusion criteria:** HBsAg positivity, HIV, Child's B or C cirrhosis **Amantadine group:** 12 patients, mean age 46 years, mean serum ALT 87 IU/L, mean viral load 83 x 10^5 eq/mL, and histological staging was 1.2. Genotype and male/female ratio were not provided **Control group:** 12 patients, mean age 46 years, mean serum ALT levels were 72 IU/L, mean viral load was 76 x 10^5 eq/mL, and histological staging was 1.4. Genotype and male/female ratio were not provided
Interventions	**Amantadine group:** interferon-alpha-2a 3 MU sc 3 times a week, and amantadine 100 mg orally twice a day for 24 weeks **Control group:** interferon-alpha-2a 3 MU sc 3 times a week for 24 weeks
Outcomes	Mortality; treatment discontinuation due to AE; number of patients without SVR; number of patients with detectable HCV RNA at EOT; number of patients without normalisation of ALT at EOT
Notes	ML sent an email to Dr. Shakil on 12 January 2012 about biochemical responses, SVR, and EOT response. Dr. Shakil responded on 13 January

	2012. ML sent another email on 26January 2012 about SAE and death. Dr. Shakil responded on 3 1January 2012 (no SAE, no death)	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information, although trial was placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information, although trial was placebo-controlled
Incomplete outcome data (attrition bias) All outcomes	High risk	Insufficient information: 2 patients in the amantadine group withdrew, 4 in the placebo group withdrew; reasons unknown
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Smith 2004

Methods	Randomised, double-blind, placebo-controlled, cross-over trial in interferon failures or those not candidates for interferon 48 weeks therapy, 24 weeks follow-up
Participants	**Country:** United States of America 152 patients were enrolled in the study **Inclusion criteria:** previous failed interferon, intolerant of interferon side effects, or not candidates for interferon therapy due to either depression, neutropenia, or thrombocytopenia. In patients who had previously been treated with interferon, a period of 6 months off therapy and a liver biopsy were required for enrolment; age between 1 and 65 years; patiens over the age of 65 years were eligible if chest x-ray, electrocardiogram, and creatinine clearance were normal prior to enrolment; abnormal liver enzymes, detectable HCV RNA; inflammation by liver biopsy; females of childbearing potential were required to use medially accepted contraceptive regimens if sexually active; normal laboratory values for albumin, prothrombin time, creatinine, haemoglobin, leukocyte count, antinuclear antibody, platelet count, and alpha-fetoprotein **Exclusion criteria:** evidence of decompensated liver disease; other forms of liver disease; active HIV infection; other serious medical conditions; active using illicit drugs or alcohol; antiviral medications, oral steroids, immunosuppressive medications, or anticoagulation therapy **Amantadine group:** 73 patients, age > 50 years, n = 13, male/female = 52/21. Serum ALT not provided and the viral load > 200 MEq/mL, n = 21. Genotype 1 (n = 57), genotype 2 (n = 9), genotype 3 (n = 6), and genotype 4 (n = 1). Histological staging: severe liver histology stage 3/4 = 34 **Control group:** 79 patients, age > 50 years, n = 18, male/female = 50/29. Serum ALT not provided and the viral load > 200 MEq/mL, n = 22. Genotype 1 (n = 59), genotype 2 (n = 9), genotype 3 (n = 5), and genotype 4 (n = 4), 2

	patients could not be genotyped by 2 separate laboratories. Histological staging: severe liver histology stage 3/4 = 39	
Interventions	**Amantadine group:** amantadine 100 mg by mouth twice daily **Control group:** placebo twice daily Both groups received amantadine or placebo for 6 months. After 6 months, patients receiving the placebo were crossed over to amantadine therapy for 6 months, while those on amantadine continued on this treatment for 6 additional months	
Outcomes	Mortality; liver-related morbidity; SAE; treatment discontinuation due to AE; QoL; number of patients without normalisation of ALT at EOT	
Notes	Amantadine was supplied by Endo Pharmaceuticals Inc. (Chadds Ford, Pa) This trial used a 5-way stratification; with this amount of patients this could lead to over-stratification ML sent an email to Dr. Smith on 9 January 2012 about exact biochemical and virological responses	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A stratified randomised scheme was invoked. SAS statistical software was used to generate the treatment codes within each of the 32 strata for implementation by the pharmacy
Allocation concealment (selection bias)	Low risk	SAS statistical software was used to generate the treatment codes within each of the 32 strata for implementation by the pharmacy
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical ghost capsules were filled by the pharmacist with amantadine and sucrose, so that neither staff nor patients could distinguish between placebo and active drug
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Identical ghost capsules were filled by the pharmacist with amantadine and sucrose, so that neither staff nor patients could distinguish between placebo and active drug
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All drop-outs were mentioned, but uncertain if they were equally divided
Selective reporting (reporting bias)	High risk	All the authors' study endpoints were discussed in the article. Not all reasonably expected outcomes were discussed
Other bias	Unclear risk	Vested interest bias: unclear No baseline imbalance; sample size calculation was reported; the trial was not stopped early

Tabone 2001

Methods	Randomised clinical trial in 9 different medical centres in naive patients Patients were enrolled between September 1998 and April 1999 12 months therapy, 6 months follow-up
Participants	**Country:** Italy 180 patients were randomised **Inclusion criteria:** positive for anti-HCV and for HCV RNA, liver biopsy within a year before entry in the study showing chronic hepatitis without cirrhosis, and serum ALT levels elevated at least 1.5 times the upper limit of normal (40 IU/L) on 3 determinations before enrolment **Exclusion criteria:** chronic alcohol abuse, active drug addiction, hepatitis B or HIV co-infection, evidence of autoimmune disease, platelet count <

	100,000/µL, leukocyte count < 2500/µL, other clinically significant diseases, and pregnancy **Amantadine group:** 90 patients, mean age 42 ± 12 years, male/female = 62/28. Serum ALT 103 (56 to 400) U/L and median basal viral load 2.4 (0.2 to 32). Genotype 1 + 4 (n = 47), genotype 2 + 3 (n = 43). Histological staging: mean 3.4 ± 0.3 **Control group:** 90 patients, mean age 44 ± 12 years, male/female = 67/23. Serum ALT 114 (65 to 274) U/L and median basal viral load 2.54 (0.2-26). Genotype 1 + 4 (n = 53), genotype 2 + 3 (n = 37). Histological staging: mean 3.2 ± 0.3	
Interventions	**Amantadine group:** interferon-alpha-2a 6 MU sc every other day for 6 months and then 3 MU sc every other day for the other 6 months plus amantadine 100 mg twice daily oral for 12 months **Control group:** interferon-alpha-2a 6 MU sc every other day for 6 months and then 3 MU sc every other day for the other 6 months	
Outcomes	Mortality; SAE; treatment discontinuation due to AE	
Notes	—	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation was centralised with a 1:1 ratio
Allocation concealment (selection bias)	Low risk	Randomisation was centralised with a 1:1 ratio
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not placebo-controlled
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-outs mentioned; 5 in control group 8 in amantadine group
Selective reporting (reporting bias)	High risk	All the authors' study endpoints were discussed in the article. Not all reasonably expected outcomes were discussed
Other bias	Low risk	Vested interest bias: no support No baseline imbalance; sample size calculation was reported; the trial was not stopped early

Teuber 2001

Methods	Randomised, placebo-controlled, double-blind trial in primary interferon-alpha in primary interferon-alpha non-responders 48 weeks therapy, 24 weeks follow-up
Participants	**Country:** Germany 55 patients were randomised **Inclusion criteria:** non-response to previous interferon-alpha monotherapy with persistence of serum HCV RNA and a treatment-free interval of at least 24 weeks; elevated ALT levels; positive anti-HCV test;

	detectable serum HCV RNA; compensated liver disease; leukocyte count ≥ 2500/µL, platelet count ≥ 70,000/µL; aged between 18 and 70 years **Exclusion criteria:** co-infection with hepatitis B and HIV, concomitant autoimmune disease, other clinically significant disease. Average daily intake of alcohol exceeding 50 g of ethanol or drug abuse within the previous year. Pregnancy and lactation period **Amantadine group:** 59 patients, mean age 47.7 ± 10.5 years, male/female = 19/7. Serum ALT 73 ± 54 U/L, serum AST 38 ± 28 U/L, and basal viral load 630 ± 567 x 10^3 copies per mL. Genotype 1 (n = 22), genotype non-1 (n = 4). Histological staging: non = 2, mild = 7, moderate = 10, severe = 7 **Control group:** 29 patients, mean age 45.7 ± 10.3 years, male/female = 17/12. Serum ALT 64 ± 44 U/L, serum AST 37 ± 25 U/L, and basal viral load 890 ± 823 x 10^3 copies per mL. Genotype 1 (n = 27), genotype non-1 (n = 2). Histological staging: non = 2, mild = 9, moderate = 12, severe = 6
Interventions	**Amantadine group:** interferon-alpha-2a 6 MU sc thrice weekly for 24 weeks, followed by 3 MU sc thrice weekly for an additional 24 weeks and oral amantadine sulphate 100 mg twice daily **Control group:** interferon-alpha-2a 6 MU sc thrice weekly for 24 weeks, followed by 3 MU sc thrice weekly for an additional 24 weeks and oral placebo twice daily
Outcomes	Mortality; liver-related morbidity; SAE; treatment discontinuation due to AE; QoL; number of patients without SVR; number of patients with detectable HCV RNA at EOT; number of patients without normalisation of ALT at EOT and at EOFU
Notes	—

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number generator in fixed blocks of 4 with a ratio of 1:1
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled with a matched placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Placebo-controlled, but insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-outs reported and equally divided over 2 groups
Selective reporting (reporting bias)	Low risk	All important outcome measures were mentioned
Other bias	Unclear risk	Vested interest bias: insufficient information No baseline imbalance; sample size calculation was not reported; the trial was not stopped early

Teuber 2002

Methods	Randomised clinical trial in relapsing patients 48 weeks therapy, 24 weeks follow-up

Participants	**Country:** Germany 75 patients were randomised. 46 males, 29 females, mean age 43 years **Inclusion criteria:** relapsing after primary successful antiviral treatment **Amantadine group:** 41 patients, mean age, male/female, serum ALT, and viral load were not provided. Genotype distribution and histological staging also were not provided **Control group:** 34 patients, mean age, male/female, serum ALT, and viral load were not provided. Genotype distribution and histological staging also were not provided
Interventions	**Amantadine group:** interferon-alpha-2b 5 MU daily for 4 weeks, 5 MU 3 times a week for 20 weeks followed by 3 MU 3 times a week for another 24 weeks in combination with daily 1000 to 1200 mg ribavirin plus 100 mg amantadine twice daily for 48 weeks **Control group:** interferon-alpha-2b 5 MU daily for 4 weeks, 5 MU 3 times a week for 20 weeks followed by 3 MU 3 times a week for another 24 weeks in combination with daily 1000 to 1200 mg ribavirin for 48 weeks Treatment was discontinued in patients with detectable serum HCV RNA after treatment week 24
Outcomes	Number of patients without SVR
Notes	ML sent an email to Dr. Teuber on 12 January 2012 about virological EOT and biochemical responses

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not placebo-controlled
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Teuber 2003

Methods	Randomised controlled trial in non-responders to previous antiviral treatment in 10 centres Patients were enrolled between July 1998 and September 1999 48 weeks therapy, 24 weeks follow-up
Participants	**Country:** Germany 225 patients were randomised

	Inclusion criteria: chronic HCV not responding to 1 or more courses of interferon-alpha with a minimal total dose of at least 108 MU for 12 weeks (e.g., at least 3 x 3 MIU tiw) alone or in combination with ribavirin and/or amantadine; documented non-response with persistently detectable serum HCV RNA during the entire, most recent antiviral treatment; treatment-free interval of at least 6 months; positive anti-HCV antibody test; detectable serum HCV-RNA; elevated ALT levels; compensated liver disease; leucocyte count ≥ 2500/µl, platelet count ≥ 70,000/µl, haemoglobin ≥12.0 g/dL in females and haemoglobin ≥13.0 g/dL in males; and patient's age ≥18 years **Exclusion criteria:** co-infection with hepatitis B virus or HIV types 1 and 2, concomitant autoimmune disease, clinically significant cardiovascular, metabolic, renal, haematological, rheumatological, neurological or psychiatric disease, systemic infections, neoplastic disease, organ grafts, systemic immunosuppressive treatment, active alcohol or drug-abuse within the previous year, pregnancy or lactation period **Amantadine group:** 115 patients, age 48 (20 to 72) year, male/female = 74/41. Median serum ALT 49 (19 to 254) U/l, median serum AST 27 (10 to 212) U/l, and median basal viral load 1.0 (0.04 to 268) x 10^6 copies per mL. Genotype 1 (n = 102) and genotype non-1 (n = 13). Histological staging (n=110): mild = 56, moderate = 40, severe = 5, and cirrhosis = 9 **Control group:** 110 patients, age 46 (24 to 71) year, male/female = 69/41. Median serum ALT 50 (18 to 762) U/l, median serum AST 28 (10- to 1206) U/l, and median basal viral load 1.0 (0.02 to 22.7) x 10^6 copies per mL. Genotype 1 (n = 97) and genotype non-1 (n = 13). Histological staging (n=105): mild = 57, moderate = 29, severe = 12, and cirrhosis = 7
Interventions	**Amantadine group:** 5 MU interferon-alpha-2b daily for the initial 4 weeks, followed by 5 MU interferon-alpha-2b thrice weekly sc for further 20 weeks and subsequently 3 MU interferon-alpha-2b thrice weekly sc for additional 24 weeks plus ribavirin 1000 to 1200 mg/day combined with amantadine sulphate 200 mg/day **Control group:** 5 MU interferon-alpha-2b daily for the initial 4 weeks, followed by 5 MU interferon-alpha-2b thrice weekly sc for further 20 weeks and subsequently 3 MU interferon-alpha-2b thrice weekly sc for additional 24 weeks plus ribavirin 1000 to 1200 mg/day After treatment week 24, antiviral treatment was only continued in patients with undetectable serum HCV RNA at treatment week 20
Outcomes	Mortality; treatment discontinuation due to AE; number of patients without SVR; number of patients with detectable HCV RNA at EOT; number of patients without normalisation of ALT at EOT and at EOFU
Notes	ML sent an email to Dr. Teuber on 11 January 2012 about SAE distribution, liver-related morbidity, and baseline characteristics

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not mentioned
Allocation concealment (selection bias)	Unclear risk	Not mentioned

Blinding of participants and personnel (performance bias) All outcomes	High risk	Not placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not placebo-controlled
Incomplete outcome data (attrition bias) All outcomes	High risk	Patients lost to follow-up were not equally divided over the 2 treatment groups. Not described why they were lost to follow-up
Selective reporting (reporting bias)	High risk	There was no protocol, but all the authors' study endpoints were discussed in the article. Not all reasonably expected outcomes were discussed nor clearly stated which groups the patients were in (for example, SAE distribution)
Other bias	Low risk	Vested interest bias: no support from pharmacy No baseline imbalance; sample size calculation was reported; the trial was not stopped early

Thuluvath 2004

Methods	Randomised, double-blind, placebo-controlled trial in naive patients in 9 centres 48 weeks therapy, 24 weeks follow-up
Participants	**Country:** United States of America 171 patients were randomised into the study **Inclusion criteria:** adult patients with chronic HCV who had no previous treatment for HCV; HCV RNA detectable by PCR, evidence of liver disease ALT or AST above the upper limit of normal, liver biopsy (within 3 months), and no known contraindications to treatment with interferon, ribavirin, or amantadine. Stress testing was required for patients at high risk for coronary artery disease, and only patients demonstrating euthyroid state were enrolled **Exclusion criteria:** haemolytic anaemia, hepatocellular carcinoma, renal failure, and seizure disorders; concomitant hepatitis B virus or HIV infection, immunosuppressed state, active substance abuse, decompensated liver disease, major psychiatric disorders, life expectancy less than 5 years, or daily alcohol intake over 10 g/day; haemoglobin < 12 g/dl, white blood cell count < 3000, platelet count < 70,000, serum bilirubin > 3 mg/dl, serum creatinine > 1.2 mg/dl, and a positive pregnancy test. Women and men of childbearing age were required to practice medically acceptable methods of contraception **Amantadine group:** 85 patients, age < 50 years: 70, age > 50 years: 15; male/female = 45/40. Serum ALT was 103 ± 126 U/L and viral load < 1 x 10^6 copies per mL: 51, viral load > 1 x 10^6 copies per mL: 34. Genotype 1a/b (n = 74), genotype 2/3 (n = 9), unable to genotype (n = 2). Histological staging: minimal/no fibrosis = 69, cirrhosis/septate fibrosis = 16 **Control group:** 86 patients, age < 50 years: 65, age > 50 years: 21; male/female = 55/31. Serum ALT was 90 ± 66 U/L and viral load < 1 x 10^6 copies per mL: 49, viral load > 1 x 10^6 copies per mL: 37. Genotype 1a/b (n = 71), genotype 2/3 (n = 13), unable to genotype (n = 2). Histological staging: minimal/no fibrosis = 64, cirrhosis/septate fibrosis = 22

Interventions	**Amantadine group:** interferon-alpha-2b sc 3 million units 3 times a week, ribavirin 1000 to 1200 mg (based on body weight) daily in divided doses, and amantadine hydrochloride 100 mg twice daily **Control group:** interferon-alpha-2b sc 3 million units 3 times a week, ribavirin 1000 to 1200 mg (based on body weight) daily in divided doses, and placebo twice daily
Outcomes	Mortality; liver-related morbidity; SAE; treatment discontinuation due to AE; number of patients without SVR; number of patients with detectable HCV RNA at EOT
Notes	ML sent an email to Dr Thuluvath about the biochemical response on 10 January 2012

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not mentioned
Allocation concealment (selection bias)	Low risk	Patients were randomly assigned (central randomisation at Johns Hopkins University)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The pharmacy department at the Johns Hopkins Hospital was responsible for randomisation and supplying amantadine or identical placebo to all centres. Unblinding of amantadine was done only when all patients completed treatment or if any patient experienced unexpected side effects (this was not necessary as there were no serious adverse events)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information, although placebo-controlled
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All drop-outs were discussed, but not clearly mentioned which patients in each group stopped for which reason
Selective reporting (reporting bias)	High risk	Not all the secondary outcome measures are well described; very sober description of ALT normalisation, no description of histological findings
Other bias	High risk	Vested interest bias: Schering-Plough No baseline imbalance; sample size calculation was reported; the trial was not stopped early

van Soest 2010

Methods	Randomised, double-blind, placebo-controlled trial in naive patients Trial duration: 52 weeks, follow-up 52 weeks Conducted from January 2001 to July 2007
Participants	**Country:** the Netherlands, 26 centres Number of patients randomised: 321, only 297 really received allocated intervention **Amantadine group:** mean age 42.6 ± 9.1 years, male/female: 108/32 **Control group:** mean age 43.8 ± 9.2 years, male/female: 105/48 **Inclusion criteria:** previously untreated adult patients who tested positive for serum HCV antibodies and HCV RNA; ALT and/or AST elevated at least once within 6 months before inclusion; liver biopsy (performed within 1 year

	before entry) consistent with chronic viral hepatitis; minimal baseline haematological values were: haemoglobin 6.5 mmol/L, white blood cells 2.5 × 10^9 L−1, neutrophils 1.5 × 10^9 L−1, platelets 70 × 10^9 L−1 and serum creatinine < 150 mol/L **Exclusion criteria:** Child-Pugh classification B or C; HIV co-infection; active uncontrolled psychiatric disorders; significant dysfunction of the central nervous system; chemotherapy and/or systemic antiviral treatment in the preceding 6 months; other serious disease; pregnancy or intention to get pregnant or unwillingness to use contraception; (former) drug users could be included if stable psychosocial situation, support and housing were available
Interventions	**Amantadine group:** peg interferon-alpha-2b, ribavirin, plus amantadine hydrochloride for 48 weeks, n = 144 **Control group:** peg interferon-alpha-2a, ribavirin, plus oral placebo of identical shape and taste was added for 48 weeks, n = 153 Both treatment groups received the same interferon-alpha induction therapy (from day 1 combined with ribavirin), consisting of interferon-alpha-2b 10 MIU/day sc during the first 6 days, followed by 5 MIU/day for the next 6 days, followed by peg interferon-alpha-2b 1.5 g/kg/week sc up to 26 weeks and 1.0 g/kg/week from week 26 to week 52. Oral ribavirin was given during the entire 52-week treatment period in 2 different doses: 1000 mg/day for body weight < 75 kg and 1200 mg/day for body weight ≥ 75 kg. In the triple therapy group, oral amantadine hydrochloride 100 mg twice daily was added
Outcomes	Sustained virological response, 1 year after cessation of the study medication; virologic response rates (negative HCV RNA at week 24); breakthrough rates (negative HCV RNA at week 24 and positive HCV RNA at week 52); relapse rates (negative HCV RNA at week 24 and 52; positive HCV RNA at week 104)
Notes	—

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Central randomisation was implemented by the pharmacist of the co-ordinating academic centre using a block size of 4
Allocation concealment (selection bias)	Low risk	Central randomisation was implemented by the pharmacist of the co-ordinating academic centre using a block size of 4
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Oral placebo of identical shape and taste
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Investigators and patients were blinded to treatment assignment during the entire study and follow-up period
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Patient withdrawal is mentioned, but the reason for withdrawal is not stated clearly for every patient
Selective reporting (reporting bias)	High risk	All outcome measures reported; lack of biochemical response
Other bias	High risk	Vested interest bias: Schering-Plough No baseline imbalance; sample size calculation was reported; the trial was not stopped early

Vardar 2001

Methods	Randomised controlled trial in naive patients in Turkey 6 months therapy, 6 months follow-up	
Participants	**Country:** Turkey 33 patients were randomised. They had biopsy-proven chronic HCV with raised ALT values equal to or greater than 1.5 times the upper normal limit, positive serum HCV RNA by PCR testing, and compensated liver disease **Amantadine group:** 19 patients, mean age, male/female, serum ALT, viral load, and histological staging were not provided. All patients had genotype 1b **Control group:** 14 patients, mean age, male/female, serum ALT, viral load, and histological staging were not provided. All patients had genotype 1b There was no difference in the means for age, sex, and initial serum transaminase values between the 2 groups	
Interventions	**Amantadine group:** interferon 3 MU 3 times per week plus amantadine 200 mg per day combination therapy for 6 months **Control group:** interferon 3 MU 3 times per week for 6 months Follow-up period was 6 months	
Outcomes	Number of patients without SVR; number of patients with detectable HCV RNA at EOT	
Notes	ML sent an email to Dr. Vardar on 12 January 2012 about biochemical responses	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not placebo-controlled
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	High risk	Only virological response
Other bias	Unclear risk	Insufficient information

von Wagner 2008

Methods	Randomised, double-blind, placebo-controlled trial in naive patients Trial duration: 48 weeks, follow-up 24 weeks
Participants	**Country:** Germany, 5 centres Number of patients randomised: 705

	Amantadine group: mean age 46.3 ± 12.0 years, male/female: 185/167 **Control group:** mean age 45.4 ± 12.2 years, male/female: 183/169 **Inclusion criteria:** male and female patients older than 18 years with compensated chronic genotype HCV-1-infection not previously treated with interferon-alpha or ribavirin; positive anti-HCV antibody and HCV RNA (600 IU/mL by quantitative RT-PCR); liver biopsy taken within 24 months before the screening visit showing chronic hepatitis; at least 1 serum ALT level elevated during the screening period; baseline neutrophil and platelet counts ≥ 1500/L and 90,000/L; haemoglobin values ≥ 12 g/dL for females and ≥ 13 g/dL for males **Exclusion criteria:** any other cause of liver disease or other relevant disorders including HIV or hepatitis B virus co-infection; other clinically significant disease; excessive daily intake of alcohol, or drug abuse within the past year; pregnancy and lactation, and male partners of pregnant women; higher degree of atrioventricular block, bradycardia (heart rate 55 beats/minute), an implanted pacemaker, prolonged Q-T-interval, or a U wave in electrocardiogram, or concomitant intake of medication with long Q-T-interval as a known side effect, concomitant medication with thiazides, known history of severe ventricular arrhythmia
Interventions	Patients were randomly assigned to receive: **Amantadine group:** amantadine-sulphate 400 mg/day orally in combination with peg interferon-alpha-2a 180 µg once per week sc plus ribavirin 1000 to 1200 mg/day orally according to body weight (75 kg: 1000 mg; 75 kg: 1200 mg), n = 353 **Control group:** placebo plus the same regimen peg interferon-alpha-2a plus ribavirin for 48 weeks, n = 352 Before onset of antiviral treatment with peg interferon-alpha-2a and ribavirin, amantadine/placebo was dose escalated within 2 weeks in 100 mg steps weekly starting at 200 mg/day
Outcomes	Sustained virological response
Notes	Additional information requested on 23 January 2012 from the last author, Prof. Dr. S. Zeuzem. Prof Zeuzem answered on 24 January with information about random sequence generation and allocation concealment. ML sent another email requesting the number of patients with liver-related morbidity. Prof. Zeuzem answered on 26 January 2012

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer random number generator
Allocation concealment (selection bias)	Low risk	Central allocation using telephone
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Placebo-controlled, but insufficient information
Blinding of outcome assessment	Unclear risk	Placebo-controlled, but insufficient information

(detection bias) All outcomes		
Incomplete outcome data (attrition bias) All outcomes	High risk	Withdrawals/loss to follow-up not equally divided
Selective reporting (reporting bias)	Unclear risk	Only 1 outcome measure, but more outcome measures reported in results. No information about histological improvement
Other bias	High risk	Vested interest bias: high: Roche No baseline imbalance; sample size calculation was not reported; the trial was not stopped early

Wenger 2007

Methods	Randomised controlled study in interferon-alpha non-responders on behalf of the Swiss Association of the Study of the Liver in 11 centres Patients were recruited between August 1999 and June 2001 48 weeks therapy, 6 months follow-up
Participants	**Country:** Switzerland 32 patients were recruited for the pilot phase, of whom 2 (1 in the triple, 1 in the combination therapy group) withdrew written consent after baseline evaluation but before starting treatment. 30 patients started the pilot phase **Inclusion criteria:** patients of both genders, aged 18 to 65 years, with chronic HCV who had previously failed to respond to interferon-alpha-2a or -2b given in a dose of 3 to 6 MU 3 times weekly for at least 12 weeks, elevated ALT within 12 months of entry on at least 2 occasions, positive HCV RNA test in serum by RT-PCR within 2 months of entry, and a liver biopsy within 5 years before entry consistent with chronic HCV **Exclusion criteria:** any other cause of liver disease including hepatitis B virus co-infection (HBsAg positive) and alcohol intake (> 20 g/day in females and > 40 g/day in males); a history of or actual decompensation of liver disease (ascites, variceal bleeding or encephalopathy); cirrhosis ≥ 8 Child-Pugh points; other clinically relevant disorders including cardiovascular, pulmonary, renal, metabolic, haematological, rheumatologic, neurological and psychiatric diseases, autoimmune disorders, HIV infection, immunosuppression within 12 months of entry, organ transplantation, malignant neoplastic disease within 2 years of study entry, illicit drug use within 1 year of study entry or psychosocial instability, pregnancy or lactation, refusal to practice effective contraception during treatment and follow-up, or treatment with any investigational drug within 6 months of study entry; leucocytes < 2000/µL, neutrophils < 1000/µL, platelets < 50,000/µL, serum creatinine > 1.5 times upper limit of normal, elevated thyroid-stimulating hormone, alfa-fetoprotein above normal limits and/or focal lesion on ultrasound performed within 1 month of study entry. **Amantadine group:** 16 patients, median age 47 (28 to 65) years, male/female = 13/3, BMI 25 (20 to 33) kg/m^2. Median serum ALT was 77 (48 to 567) U/l and the median basal viral load was 4.3 (0.16 to 25) x 10^6 copies per mL. Genotype 1 + 4 (n = 9) and genotype 2 + 3 (n = 7). Histological staging: 3 patients had cirrhosis **Control group:** 14 patients, median age 45 (23 to 59) years, male/female = 12/2, BMI 26 (21 to 40) kg/m^2. Median serum ALT was 89 (53 to 397) U/l and the median basal viral load was 2.0 (0.12 to 26.2) x 10^6 copies per mL. Genotype 1 + 4 (n = 11) and genotype 2 + 3 (n = 3). Histological staging: 1 patient had cirrhosis Sample size calculation was not mentioned

Interventions	**Amantadine group:** interferon-alpha-2a 6 MIU sc daily for 4 weeks, followed by 6 MIU sc tiw for an additional 44 weeks, ribavirin (< 75 kg: 1000, ≥ 75 kg: 1200 mg), plus amantadine sulphate 100 mg po twice daily **Control group:** interferon-alpha-2a plus ribavirin in the above mentioned doses Treatment was stopped, if after 4 weeks HCV RNA in serum remained detectable by RT-PCR (detection limit: 1000 copies/mL) Patients were followed for 24 weeks after stopping therapy	
Outcomes	Mortality; liver-related morbidity; SAE; treatment discontinuation due to AE; number of patients without SVR; number of patients with detectable HCV RNA at EOT; number of patients without normalisation of ALT at EOT and at SVR	
Notes	ML sent an email about the biochemical response at EOT and 24 weeks after stopping therapy to Dr. Beat Mullhaupt on10 January 2012. Dr. Mullhaupt responded on 11 January 2012 with the following information: biochemical response at EOT in the triple therapy 4 out of 16, sustained biochemical response 3 out of 16. In the double therapy arm EOT was 3 out of 14, as well as the sustained biochemical response	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Patients were randomised with a ratio of 1:1. Randomisation was carried out in blocks of 10 using random numbers
Allocation concealment (selection bias)	Unclear risk	Insufficient information, method is not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not placebo-controlled
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-outs were discussed
Selective reporting (reporting bias)	High risk	No ALT description and no QoL description, although mentioned as endpoint in the methods section
Other bias	High risk	Vested interest bias: interferon-alpha-2a (Roferon® A), ribavirin and amantadine sulphate (PK Merz®) were provided by Roche Pharma (Schweiz) AG, Reinach, Switzerland Baseline balance is questionable: baseline variables were similar in both groups, except genotype 1 and 4 infection and cirrhosis tended to be slightly more prevalent in the double and triple therapy group. No baseline imbalance; sample size calculation was not reported; the trial was not stopped early

Yang 2003

Methods	Randomised, double-blind, placebo-controlled trial in naive patients Patients were studied between October 1996 and October 1998 24 weeks therapy, 1 year follow-up	
Participants	**Country:** Taiwan, 1 centre Number of patients randomised: 30 Amantadine group n = 15: age 42 ± 9 years, male/female: 12/3 Control group n = 15: age 38 ± 7 years, male/female: 12/3 **Inclusion criteria:** naive patients aged between 20 and 55 years; positive for anti-HCV antibodies; abnormal serum ALT levels for more than 6 months, at least 3 documented occasions higher than twice the upper limit of normal (< 3 IU/L) with 1 month apart, within 6 months prior to enrolment; liver biopsy, within 1 month before start of treatment, to confirm chronic hepatitis without cirrhosis **Exclusion criteria:** alcoholic, no intravenous drug abusers or homosexuals; hepatotoxic drugs, herb medicine, and immunosuppressive therapy within the past 6 months; decompensated liver function, cirrhosis; other diseases, i.e., chronic renal failure, neurological disorders, chronic hepatitis B, autoimmune; pregnancy; white cells and platelet abnormalities	
Interventions	Patients were randomly assigned to receive: **Amantadine group:** 4.5 MU recombinant interferon-alpha-2a sc thrice weekly and oral amantadine twice daily 100 mg, n = 15 **Control group:** 4.5 MU recombinant interferon-alpha-2a sc thrice weekly and oral placebo twice daily for 24 weeks, n = 15	
Outcomes	Complete response: normalisation of serum ALT levels together with the absence of serum HCV RNA by the end of treatment = composite outcome; sustained complete response: the continuation of the remission 12 months after the end of treatment	
Notes	Additional information requested on 23 January 2012 to the first author Dr. S. Yang. Dr. Yang answered on 27 January 2012	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer random number generator
Allocation concealment (selection bias)	Low risk	By pharmacy. Only the pharmacologist in charge knew the sequence. The patients received amantadine or placebo from the pharmacy
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information, although placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information, although placebo-controlled

Incomplete outcome data (attrition bias) All outcomes	Low risk	1 patient lost to follow-up 2 months after treatment. All others finished follow-up period
Selective reporting (reporting bias)	High risk	No information about separate biochemical outcome
Other bias	Unclear risk	Vested interest bias: unknown No baseline imbalance; sample size calculation was not reported; the trial was not stopped early

Zeuzem 2000

Methods	Randomised, double-blind, placebo-controlled trial in naive patients in Germany Patients were enrolled between March and October 1997 48 weeks therapy, 24 weeks follow-up	
Participants	**Country:** Germany 120 patients were enrolled, 1 patient did not receive treatment. 119 started treatment **Inclusion criteria:** patients aged 18 to 70 years with compensated chronic, HCV infection not previously treated with interferon, ribavirin, and/or amantadine. Tested positive for anti-HCV and HCV RNA by RT-PCR. A liver biopsy within a year of study entry showing chronic hepatitis, and had elevated serum ALT levels for at least 6 months before initiation of treatment. Entry leucocyte count had to be ≥ 2500/µL, platelets > 70,000/µL **Exclusion criteria:** any other cause of liver disease or other relevant disorders, including HIV or hepatitis B co-infection. Evidence or history of autoimmune disease. Other clinically significant diseases. Average daily intake of alcohol exceeding 50 g of ethanol or drug abuse within the previous year. Pregnancy and lactation period **Amantadine group:** 26 patients, mean age 42.1 ± 12.9 years, male/female = 37/22. Serum ALT was 57.5 ± 39.0 U/L and the basal viral load was 7.8 ± 8.5 x 10^6 copies per mL. Genotype 1 (n = 42), genotype 2 (n = 3), genotype 3 (n = 13), genotype 4 (n = 1). Histological staging: non = 8, mild = 25, moderate = 18, severe = 8 **Control group:** 60 patients, mean age 41.6 ± 10.3 years, male/female = 36/24. Serum ALT was 59.6 ± 36.0 U/L and the basal viral load was 7.4 ± 9.8 x 10^6 copies per mL. Genotype 1 (n = 40), genotype 2 (n = 3), genotype 3 (n = 15), genotype 4 (n = 1). Histological staging: non = 2, mild = 28, moderate = 22, severe = 8	
Interventions	**Amantadine group:** interferon-alpha-2a 6 MU sc thrice weekly for 24 weeks, followed by 3 MU sc thrice weekly for an additional 24 weeks and amantadine sulphate 100 mg po twice daily **Control group:** interferon-alpha-2a 6 MU sc thrice weekly for 24 weeks, followed by 3 MU sc thrice weekly for an additional 24 weeks and placebo po twice daily	
Outcomes	Mortality; SAE; treatment discontinuation due to AE; QoL; number of patients without SVR; number of patients with detectable HCV RNA at EOT; number of patients without improvement of histology; number of patients without normalisation of ALT at EOTand at EOFU	
Notes	—	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Random sequence generation (selection bias)	Low risk	Random number generator in fixed blocks of 4 with a ratio of 1:1
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled with matched placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Placebo-controlled, but insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data, equally divided
Selective reporting (reporting bias)	Low risk	No selective reporting
Other bias	High risk	Vested interest bias: Merz + Roche No baseline imbalance; sample size calculation was reported; the trial was not stopped early

AE: adverse event
ALT: alanine aminotransferase
AST: aspartate transaminase
bid: twice a day
BMI: body mass index
EDLQ: everyday life questionnaire
ELISA: enzyme-linked immunosorbent assay
EOFU: end of follow-up
EOT: end of treatment
EVR: early virological response
HAI: histology activity index
HAV: hepatitis A virus
HBsAg: hepatitis B surface antigen
HBV: hepatitis B virus
HCV: hepatitis C virus
HIV: human immunodeficiency virus
HRQoL: health-related quality of life
ITT: intention-to-treat
MIU: million international units
MU: million units
NS: non-significant
PCR: polymerase chain reaction
po: orally
POMS: profile of mood status scale
QoL: quality of life
RNA: ribonucleic acid
RT-PCR: real-time polymerase chain reaction
SAE: serious adverse event
sc: subcutaneous
SVR: sustained virological response
tiw: three times weekly
U/L: units per liter
VAS: visual analogue scale
WBC: white blood cells

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Buggisch 2009	Unknown how many patients were randomised to each group
Di Bisceglie 2001	Compared amantadine plus peg interferon-alpha and ribavirin with amantadine and peg interferon-alpha
Mendez-Navarro 2010a	Not randomised: erratum
Nakamura 2003	Not randomised
Popovic 2000	Data in text and table are not comparable and reproducible
Quarantini 2006	Does not report one of our outcome measures
Schories 2003	Does not report one of our outcome measures
Torre 1999	Does not report one of our outcome measures
Zilly 2002	Not randomised

Reference list

References to studies included in this review

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5

Aminoadamantanes versus other antiviral drugs for chronic hepatitis C

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Abstract

Background: Hepatitis C virus infection affects around 3% of the world population or approximately 160 million people. A variable proportion (5% to 40%) of the infected people develop clinical symptoms. Hence, hepatitis C virus is a leading cause of liver-related morbidity and mortality with hepatic fibrosis, end-stage liver cirrhosis, and hepatocellular carcinoma as the dominant clinical sequelae. Combination therapy with pegylated (peg) interferon-alpha and ribavirin achieves sustained virological response (that is, undetectable hepatitis C virus RNA in serum by sensitivity testing six months after the end of treatment) in approximately 40% to 80% of treated patients, depending on viral genotype. Recently, a new class of drugs have emerged for hepatitis C infection, the direct acting antivirals, which in combination with standard therapy or alone can lead to sustained virological response in 80% or more of treated patients. Aminoadamantanes, mostly amantadine, are antiviral drugs used for the treatment of patients with chronic hepatitis C. We have previously systematically reviewed amantadine versus placebo or no intervention and found no significant effects of the amantadine on all-cause mortality or liver-related morbidity and on adverse events in patients with hepatitis C. Overall, we did not observe a significant effect of amantadine on sustained virological response. In this review, we systematically review aminoadamantanes versus other antiviral drugs.

Objectives: To assess the beneficial and harmful effects of aminoadamantanes versus other antiviral drugs for patients with chronic hepatitis C virus infection by conducting a systematic review with meta-analyses and trial sequential analyses of randomised clinical trials.

Search methods: The Cochrane Hepato-Biliary Group Controlled Trials Register (1996 to December 2013), the Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 11 of 12, 2013), MEDLINE (1946 to December 2013), EMBASE (1974 to December 2013), Science Citation Index EXPANDED (1900 to December 2013), the WHO International Clinical Trials Registry Platform (www.who.int/ictrp), Google Scholar, and Eudrapharm up to December 2013. Furthermore, full text searches were conducted until December 2013.

Selection criteria: Randomised clinical trials assessing aminoadamantanes in participants with chronic hepatitis C virus infection.

Data collection and analysis: Two authors independently extracted data. RevMan Analysis was used for statistical analysis of dichotomous data using risk ratio (RR) with 95% confidence

intervals (CI). Methodological domains were used to assess the risk of systematic errors ('bias'). We used trial sequential analysis to assess risk of random errors ('play of chance').

Main results: Six randomised clinical trials with 581 participants with chronic hepatitis C were included. All trials had high risk of bias. The included trials compared amantadine versus other antiviral drugs: ribavirin, mycophenolate mofetil, interferon-alpha, or interferon-gamma. Standard antiviral therapy (interferon-alpha, interferon-alpha plus ribavirin, or peg interferon alpha) was administered equally to the intervention and the control groups in five trials, depending on when the trial was conducted. Four trials compared amantadine versus ribavirin. There were no deaths or liver-related morbidity in the two intervention groups (0/216 (0%) versus 0/211 (0%); 4 trials; very low quality of the evidence). The lower estimated risk for (serious) adverse events leading to treatment discontinuation with amantadine was imprecise (RR 0.56, 95% CI 0.27 to 1.16; based on 10/216 (5%) versus 18/211 (9%) participants in 4 trials; very low quality of the evidence). There were more participants with failure of sustained virological response in the amantadine group than in the ribavirin group (206/216 (96%) versus 176/211 (84%); RR 1.14, 95% CI 1.07 to 1.22, 4 trials; low quality of the evidence). Amantadine versus ribavirin more often failed to achieve end-of follow-up biochemical response (41/46 (89%) versus 31/46 (67%); RR 1.31, 95% CI 1.05 to 1.63; 2 trials; very low quality of the evidence). One trial compared amantadine versus mycophenolate mofetil. There were no significant differences between the two treatment groups, except that amantadine was inferior to mycophenolate mofetil regarding the outcome failure to achieve end-of treatment virological response (low quality of evidence). One trial each compared amantadine versus interferon-alpha or interferon-gamma. Both comparisons showed no significant differences in the treatment outcomes (very low quality of the evidence). The observed effects could be due to real effects, systematic errors (bias), or random errors (play of chance). This possible influence on the observed effect by play of chance is due to the fact that trial sequential analyses could not confirm our findings. We were not able to perform meta-analyses on failure of histological improvement and quality of life due to lack of valid data in all trial comparisons.

Authors' conclusions: This systematic review has identified evidence of very low quality for the key outcomes of all-cause mortality or liver-related morbidity and adverse events in people with chronic hepatitis C when treated with amantadine compared with ribavirin, mycophenolate, interferon-alpha, or interferon-gamma. The timeframe for measuring the composite outcome was insufficient in the included trials. There was low quality evidence that amantadine led to more participants who failed to achieve sustained virological response compared with ribavirin. This observation may be real or caused by systematic errors (bias),

but it does not seem to be caused by random error (play of chance). Due to the low quality of the evidence, we are unable to determine definitively whether amantadine is less effective than other antivirals in patients with chronic hepatitis C. As it appears less likely that future trials assessing amantadine or potentially other aminoadamantanes for patients with chronic hepatitis C would show strong benefits, it is probably better to focus on the assessments of other direct acting antiviral drugs. We found no evidence assessing other aminoadamantanes in randomised clinical trials in order to recommend or refute their use.

Summary of findings

Summary of findings for the main comparison.

Aminoadamantanes compared with ribavirin for chronic hepatitis C					
Patient or population: patients with chronic hepatitis C. **Settings:** mainly outpatients in tertiary and teaching hospitals. **Intervention:** aminoadamantanes. **Comparison:** ribavirin.					
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**
	Assumed risk	**Corresponding risk**			
	Ribavirin	**Aminoadamantanes**			
All-cause mortality or liver-related morbidity Follow-up: 12-24 months	**Study population**		**RR 0.98** (0.00 to 248.89)	427 (4 trials)	⊕⊖⊖⊖ **very low[1]**
	0 per 1000	**0 per 1000** (0 to 0)			
Adverse events Follow-up: 12-24 months	**Study population**		**RR 0.56** (0.27 to 1.16)	427 (4 trials)	⊕⊖⊖⊖ **very low[1]**
	86 per 1000	**47 per 1000** (23 to 98)			
Failure of sustained virological response Absence of clearance of HCV RNA from the blood 6 months after treatment Follow-up: 12-24 months	**Study population**		**RR 1.14** (1.07 to 1.22)	427 (4 trials)	⊕⊕⊕⊖ **low[2]**
	835 per 1000	**954 per 1000** (896 to 1021)			
Failure of end of treatment	**Study population**		**RR 1.20**	309 (3 trials)	⊕⊕⊖⊖ **low[2]**
	678 per 1000	**816 per 1000** (714 to 925)			

virological response Absence of clearance of HCV RNA from the blood at end of treatment Follow-up: 12-24 months			(1.05 to 1.36)		
Failure of normalisation of ALT at end of treatment Follow-up: 12-24 months	**Study population**		**RR 2.02** (1.07 to 3.82)	29 (1 trial)	⊕⊖⊖⊖ **very low**[1]
	429 per 1000	**867 per 1000** (460 to 1640)			
Failure of normalisation of ALT at end of follow-up Follow-up: 12-24 months	**Study population**		**RR 1.31** (1.05 to 1.63)	92 (2 trials)	⊕⊖⊖⊖ **very low**[1]
	674 per 1000	**892 per 1000** (715 to 1110)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

ALT: alanine aminotransferase; **CI:** confidence interval; **HCV:** hepatitis C virus; **RNA:** ribonucleic acid; **RR:** risk ratio.

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

Background

Description of the condition

Hepatitis C virus was first described in 1989 (Choo 1989). It affects around 3% of the world population, thus affecting approximately 160 million people (Sy 2006; Lavanchy 2011). Hepatitis C virus is a leading cause of mortality and liver-related morbidity with hepatic fibrosis, liver cirrhosis, and hepatocellular carcinoma as the dominant clinical sequelae (Sy 2006). Hepatocellular carcinoma occurs in 3 per 100,000 persons in the United States of America (El-Serag 2003). Hepatitis C virus is responsible for one-third of these hepatocellular carcinomas (El-Serag 2003). In cirrhotic hepatitis C virus patients, the annual occurrence of hepatocellular carcinoma is 1% to 4% (Lauer 2001). Furthermore, hepatitis C virus infection is the most common indication for orthotopic liver transplantation (Kim 2009).

Chronic hepatitis C virus progresses slowly, over a time frame of 15 years to 50 years. Prospective and retrospective studies following cohorts of patients for decades suggested that less than 10% of all infected individuals would develop end-stage liver disease. However, there are also publications reporting on patients who had developed cirrhosis two or three decades after infection with a range of 0.5% to 39% (Koretz 1993; Kenny-Walsh 1999; Rodger 2000; Wiese 2000; Thein 2008; Seeff 2009).

Hepatitis C virus is divided into six genotypes (from 1 to 6) (Simmonds 2005). Genotypes 1 to 4 are the most common genotypes (Simmonds 2005). Several factors have an influence on achieving a sustained virological response to antiviral drugs (that is, undetectable hepatitis C virus ribonucleic acid (RNA) in serum by sensitivity testing six months after the end of treatment); genotype is one of these factors (Asselah 2010). Genotypes 2 and 3 respond better to treatment than genotypes 1 and 4 (Asselah 2010).

In 1990, interferon-alpha, an antiviral drug, was approved for the treatment of chronic hepatitis C virus as monotherapy (Tine 1991). Interferon-alpha was administered subcutaneously in doses of equal to or more than three million units (MU) in the induction phase (during one to three months) and less than three MU in the maintenance phase (Tine 1991). Results of studies showed that only 10% to 17% of patients responded to interferon-alpha monotherapy in achieving a sustained virological response compared with 1% to 3% of participants on no intervention (Davis 1989; Myers 2002).

Antiviral drugs for patients with hepatitis C virus-related liver disease have improved considerably during the past two decades (Ghany 2009). In 1998, trials assessed the combination of interferon-alpha and ribavirin compared with interferon alpha alone (Davis 1998; McHutchison 1998; Poynard 1998). This combination treatment resulted in an improved antiviral response in naive, chronic hepatitis C virus-infected patients compared with interferon-alpha alone (Brok 2010), and in previously treated patients who had failed to respond to interferon-alpha monotherapy (Brok 2010).

The success of antiviral therapy is usually defined as the proportion of patients who achieve sustained virological response, that is, clearance of hepatitis C virus RNA from the blood six months after treatment. Observational studies have suggested that people with sustained virological response have less disease progression and less risk of hepatocellular carcinoma (Ueno 2009). However, following a systematic review of meta-analyses with randomised clinical trials comparing ribavirin plus interferon-alpha versus interferon-alpha alone, this drug therapy combination seemed to result in more patients with a sustained virological response, but no conclusion could be made if this combination results in less mortality or morbidity (Brok 2010). Sustained virological response is still a non-validated putative surrogate outcome measure (Gluud 2007).

A recent trial showed that there was an increased mortality in patients who were retreated with interferon-alpha compared with non-treated patients (Di Bisceglie 2011) and that was supported in a Cochrane systematic review (Koretz 2013).

The current standard of treatment for chronic hepatitis C virus infection, according to guidelines, is a combination of pegylated interferon-alpha (peg interferon-alpha) and ribavirin (Ghany 2009; EASL 2014). The regimen can include either peg interferon-alpha-2b (Peg-Intron®, Schering Plough Corp., Kenilworth, NJ) or peg interferon-alpha-2a (Pegasys®, Hoffmann-La Roche, Nutley, NJ), both of which are administered subcutaneously (Awad 2010). The optimal dose of peg interferon-alpha-2b is 1.5 µg/kg/week (Awad 2010; Hauser 2014a). Peg interferon-alpha-2a is administered at a fixed dose of 180 µg weekly (Awad 2010). Ribavirin is an oral therapy with weight-based total daily doses between 800 mg to 1200 mg administered twice per day (Brok 2009). Between 40% and 80% of chronic hepatitis C virus patients without co-infection with hepatitis B virus or human immunodeficiency virus (HIV) will achieve a sustained virological response after treatment with peg interferon-alpha and ribavirin (Simin 2007; Awad 2010; Hauser 2014; Hauser 2014a).

Recently, a new class of antiviral drugs for hepatitis C virus have emerged on the market. These antiviral agents act directly, inhibiting the nonstructural (NS) NS3/N4A serine protease and NS5B polymerase inhibitors of hepatitis C virus. The direct acting antivirals can alone, or in concert with peg interferon-alpha and ribavirin (triple therapy) increase sustained virological response proportions to 80% or above (Bacon 2011; Jacobson 2011; Poordad 2011; Sherman 2011; Zeuzem 2011; Lawitz 2013; Lawitz 2014; Sulkowski 2014). The effects they show on sustained virological response will hopefully lead to comparable clinical responses.

Description of the intervention

Aminoadamantanes is another antiviral drug group which includes amantadine and rimantadine. The drugs have been investigated in several studies for treatment of patients with chronic hepatitis C virus (Brillanti 1999; Smith 2004). These aminoadamantanes were investigated as oral monotherapy, administered mostly as 100 mg twice a day, and also in combination with interferon-alpha or ribavirin, or both. The benefits and harms of aminoadamantanes compared with placebo in patients with chronic hepatitis C virus infection have been explored in a meta-analysis by Deltenre 2004 and in a recent Cochrane systematic review (Lamers 2014).

How the intervention might work

Aminoadamantanes have been used for many years to prevent infection with influenza and have been shown to have activity against *Flaviviridae, a* family of viruses, encompassing hepatitis C virus infection (Koff 1980). Known mechanisms of action of aminoadamantanes include inhibition of an early step in viral replication, most likely viral uncoating and interaction with the influenza A viral matrix protein (M2), which is important in virion budding (De Clercq 2001). The aminoadamantane such as amantadine acts similar to ribavirin; ribavirin in monotherapy often improves liver biochemistry (Reichard 1991; Reichard 1993), but seems to have no major effect in the course of hepatitis C virus infection on its own (Brok 2009). However, it is unclear whether aminoadamantanes may reduce the hepatitis C virus viral load or improve liver biochemistry (Lamers 2014).

Why it is important to do this review

The combination therapy of peg interferon-alpha and ribavirin yields sustained virological response in approximately 40% to 80% of treated patients (Simin 2007; Awad 2010). This indicates an unmet need for drugs in order to reach higher proportions of sustained virological response. With the new direct antiviral agents, higher proportions can be achieved (Bacon

2011; Jacobson 2011; Poordad 2011; Sherman 2011; Zeuzem 2011). Several studies have been published regarding the effect of aminoadamantanes. Our systematic review is aimed at assessing the benefits and harms of aminoadamantanes versus other antiviral drugs. This systematic review may have practical implications on the way patients with chronic hepatitis C virus should be treated.

The benefits and harms of aminoadamantanes compared with placebo and other antiviral drugs in patients with chronic hepatitis C virus infection have been explored earlier in a meta-analysis by Deltenre 2004. A recent Cochrane systematic review compared aminoadamantanes with placebo for chronic hepatitis C (Lamers 2014). We found no significant effect of amantadine when compared with placebo or no intervention on sustained virological response or clinical outcomes (Lamers 2014).

Objectives

To explore the beneficial and harmful effects of aminoadamantanes versus other antiviral drugs for patients with chronic hepatitis C virus infection in a systematic review with meta-analysis and trial sequential analysis of randomised clinical trials.

Methods

Criteria for considering studies for this review

Types of studies

Randomised clinical trials assessing aminoadamantanes compared with other antiviral drugs in participants with chronic hepatitis C virus infection irrespective of duration of treatment, language, publication type and status, and blinding. Quasi-randomised studies or other observational studies captured during the search process were excluded for the report of benefit but were reported in a narrative way for the data on harm from such studies.

Types of participants

We included participants with chronic hepatitis C virus. The diagnosis was based on the presence of serum hepatitis C virus RNA (HCV RNA) plus elevated transaminases for more than six months, or chronic hepatitis documented on liver biopsy. We also included participants

diagnosed with 'non-A, non-B' chronic hepatitis as some trials may have been conducted before HCV RNA analyses were widely available.

Based on the existence of, and response to previous antiviral treatment, we classified the included participants as naive (not previously treated with antivirals), relapsers (participants with a transient serological viral response to previous treatment with antivirals), or non-responders (patients without serological viral response to previous treatment with antivirals). We excluded participants who had undergone liver transplantation.

Types of interventions

Aminoadamantanes versus other antiviral drugs.
Co-interventions were allowed if administered equally to the intervention groups being compared.

Types of outcome measures

Primary outcomes

1. All-cause mortality or liver-related morbidity as a composite outcome: number of patients who died or who developed, for example, cirrhosis, ascites, hepatic encephalopathy, or hepatocellular carcinoma.
2. Adverse events: number of patients with either serious adverse events or treatment discontinuation due to any adverse event. Serious adverse events are defined according to the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice as "any untoward medical occurrence that at any dose resulted in death, was life-threatening, required inpatient hospitalisation or prolongation of existing hospitalisation, or resulted in persistent or significant disability or incapacity, or was a congenital anomaly/birth defect, or any medical event that might have jeopardised the patient, or required intervention to prevent it" (ICH-GCP 1997). All other adverse events (that is, any medical occurrence not necessarily having a causal relationship with the treatment but that did, however, cause a dose reduction or discontinuation of the treatment) were considered as being non-serious (ICH-GCP 1997).
3. Quality of life (as reported in the trials).

Secondary outcomes

1. Failure of serum (or plasma) sustained virological response: number of patients with detectable HCV RNA at least six months after treatment.
2. Failure of end-of treatment virological response: number of patients with detectable HCV RNA at the end of treatment.
3. Failure in histological response: number of patients without improvement of histology (inflammation score (grading) or fibrosis score (staging) as defined by the individual trials).
4. Number of participants without normalisation of alanine aminotransferase (ALT) or aspartate transaminase (AST) serum levels or both (defined by the individual trials) at end of treatment and end of follow-up.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Hepato-Biliary Group Controlled Trials Register (1996 to December 2013) (Gluud 2014), the Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 11 of 12, 2013), MEDLINE (1946 to December 2013), EMBASE (1974 to December 2013), and Science Citation Index EXPANDED (1900 to December 2013) (Royle 2003). We also searched the WHO International Clinical Trials Registry Platform (www.who.int/ictrp), Google Scholar, and Eudrapharm. We have given the search strategies in Appendix 1 with the time spans of the searches.

Searching other resources

We identified further trials by reading the reference lists of the identified studies. We checked review articles and meta-analyses in order to find randomised trials not identified by the electronic searches. We searched for abstracts from various gastrointestinal meetings. We wrote to the principal authors of the identified randomised trials and to the researchers active in the field to enquire about additional randomised trials they might know of. In order to obtain unpublished trials, we contacted pharmaceutical companies involved in the production and assessment of aminoadamantanes.

Data collection and analysis

Selection of studies

Two review authors (ML, MB) independently inspected each reference identified by the searches and applied the inclusion criteria. For possible relevant publications, or in cases of disagreement between the two review authors, the full article was obtained and inspected independently by the two authors. If the two review authors still disagreed, a third review author (CG) was consulted.

Data extraction and management

Two review authors (ML, MB) independently extracted data. In case of disagreement between the two review authors, a third review author (CG) arbitrated. The data extraction was discussed, decisions documented, and, where necessary, we contacted trial authors for clarification. Trials were identified by the name of the first author and year in which the study was published in full and ordered chronologically.

The following data were extracted, checked, and recorded.

- Characteristics of trials: date, location and setting; publication status; sponsor (specified, known or unknown); duration of follow-up; bias-domains; sample size calculation.
- Characteristics of participants: number of participants in each group; age; sex; ethnicity; weight or body mass index; viral load at the beginning of treatment; degree of fibrosis at the beginning of treatment.
- Characteristics of interventions: dose and duration of aminoadamantanes and any co-interventions.
- Characteristics of outcome measures: whenever possible, the number of events previously listed under 'outcome measures' were recorded in each group of the trial; information about harms were extracted in observational studies.

Assessment of risk of bias in included studies

According to empirical evidence (Schultz 1995; Moher 1998; Kjaergard 2001; Wood 2008; Lundh 2012; Savović 2012; Savović 2012a), risk of bias in a trial can be assessed using 'Risk of bias' domains. We have used the following domains with definitions to assess the risk of bias of the trials included in the review.

Allocation sequence generation

- Low risk of bias: sequence generation was achieved using computer random number generation or a random number table. Drawing lots, tossing a coin, shuffling cards, and throwing dice are adequate if performed by an independent person not otherwise involved in the trial.
- Uncertain risk of bias: the method of sequence generation was not specified.
- High risk of bias: the sequence generation method was not random.

Allocation concealment

- Low risk of bias: the participant allocations could not have been foreseen in advance of, or during, enrolment. Allocation was controlled by a central and independent randomisation unit. The allocation sequence was unknown to the investigators (for example, if the allocation sequence was hidden in sequentially numbered, opaque, and sealed envelopes).
- Uncertain risk of bias: the method used to conceal the allocation was not described so that intervention allocations may have been foreseen in advance of, or during, enrolment.
- High risk of bias: the allocation sequence was likely to be known to the investigators who assigned the participants.

Blinding of participants, personnel, and outcome assessors

- Low risk of bias: blinding was performed adequately, or the assessment of outcomes was not likely to be influenced by lack of blinding.
- Uncertain risk of bias: there was insufficient information to assess whether blinding was likely to induce bias on the results.
- High risk of bias: no blinding or incomplete blinding, and the assessment of outcomes was likely to be influenced by lack of blinding.

Incomplete outcome data

- Low risk of bias: missing data were unlikely to make treatment effects depart from plausible values. Sufficient methods, such as multiple imputation, have been employed to handle missing data.
- Uncertain risk of bias: there was insufficient information to assess whether missing data in combination with the method used to handle missing data were likely to induce bias on the results.

- High risk of bias: the results were likely to be biased due to missing data.

Selective outcome reporting

- Low risk of bias: all outcomes were pre-defined and reported, or all clinically relevant and reasonably expected outcomes were reported.
- Uncertain risk of bias: it is unclear whether all pre-defined and clinically relevant and reasonably expected outcomes were reported.
- High risk of bias: one or more clinically relevant and reasonably expected outcomes were not reported, and data on these outcomes were likely to have been recorded.

For a trial to be assessed with low risk of bias in the selective outcome reporting domain, the trial should have been registered either on the www.clinicaltrials.gov web site or a similar register, or there should be a protocol, for example published in a paper journal. In the case where the trial was run and published in the years when trial registration was not required, we carefully scrutinised all publications reporting on the trial to identify the trial objectives and outcomes. If usable data on all outcomes specified in the trial objectives were provided in the publication's results section, then the trial can be considered low risk of bias in the 'Selective outcome reporting' domain.

For-profit bias

- Low risk of bias: the trial appeared to be free of industry sponsorship or other kind of for-profit support that might have result in manipulation of the trial design, conduct, or results of the trial.
- Uncertain risk of bias: the trial might or might not be free of for-profit bias as no information on clinical trial support or sponsorship is provided.
- High risk of bias: the trial was sponsored by industry or had received other kinds of for-profit support.

All trials were assessed for risk of bias. If the risk of bias in a trial was judged as 'low' in all the above listed domains, then the trial was considered at 'low risk of bias'. If the risk of bias was judged as 'uncertain' or 'high', then the trial was considered at 'high risk of bias'.

Reporting bias was handled following the recommendations of The Cochrane Collaboration (Higgins 2011). Subgroup analyses (see below) and funnel plot asymmetry were assessed (Higgins 2011), even though asymmetric funnel plots are not necessarily caused by publication bias and publication bias does not necessarily cause asymmetry in a funnel plot (Egger 1997).

Measures of treatment effect

The treatment effects in this meta-analysis are dichotomous or continuous. The dichotomous data were expressed with risk ratio (RR) and 95% confidence intervals (CI). The number needed to treat (NNT) was derived from the risk difference (RD), in case the intervention effect was considered significant and valid. For continuous data, we planned to use the mean difference when outcomes of the trials were measured in the same way. Where appropriate, we would have used the standardised mean difference to combine trials that measured the same outcome but used different methods.

Unit of analysis issues

We used the intervention groups of participants in randomised clinical trials as our unit of analysis. Three included trials used a two-armed parallel group design; the other three trials used a multiple-armed parallel group design. We present those additional treatment arms in the 'Summary of characteristics of included studies', see Table 1. Where the additional treatment arms were not relevant, we did not use these data.

Table 1. Summary of characteristics of the included trials

Trial	Risk of bias	Trial duration (months)	Follow-up duration (months)
Amantadine versus ribavirin			
Khalili 2000	High	6	6
Younossi 2001	High	6	6
Herrine 2005	High	12	6
Salmeron 2007	High	12	6
Amantadine versus mycophenolate mofetil			
Herrine 2005	High	12	6
Amantadine versus interferon-alpha			
Bacosi 2002	High	12	12
Amantadine versus interferon-gamma			
Abbas 2012	High	12	6

Dealing with missing data

We contacted the original investigators to request missing data that we expected to have been measured but were not reported.

We performed all analyses according to the intention-to-treat method, including all participants irrespective of compliance or follow-up.

Regarding our primary outcomes, we included patients with incomplete or missing data in sensitivity analyses by imputing them according to the following two extreme scenarios (Hollis 1999; Gluud 2014).

- Extreme case analysis favouring the experimental intervention ('best-worse' case scenario): none of the dropouts/participants lost from the experimental arm, but all of the dropouts/participants lost from the control group experienced the outcome, including all randomised participants in the denominator.
- Extreme case analysis favouring the control ('worst-best' case scenario): all dropouts/participants lost from the experimental arm, but none from the control arm experienced the outcome, including all randomised participants in the denominator.

Assessment of heterogeneity

We assessed heterogeneity using the chi-squared statistic test of heterogeneity and quantity of heterogeneity by the I^2 measure of inconsistency (Higgins 2011). In case of substantial heterogeneity as measured by a chi-square test P value less than 0.1 or an I^2 measure greater than 70%, we considered not to conduct the meta-analysis. We assessed sources of clinical, methodological, and statistical heterogeneity in subgroup analyses.

Assessment of reporting biases

Described under 'Assessment of risk of bias in included studies'.

Data synthesis

Meta-analysis

For the statistical analyses, we used Review Manager 5.2 (RevMan 2012). We meta-analysed the data with both a random-effects model (DerSimonian 1986) and a fixed-effect model (DeMets 1987) to ensure robustness of the results. In case of statistically significant differences of the results that the two methods produced, we presented the results with both methods. If there were no differences in the results, we presented the results of the fixed-effect model only (Higgins 2011). If there was considerable variation in the results, and particularly if the direction of effect was inconsistent, it may be misleading to quote the

average value for the intervention effect; we therefore interpreted the meta-analyses with utmost care.

Trial sequential analysis

We applied trial sequential analysis (CTU 2011; Thorlund 2011) as cumulative meta-analyses are at risk of producing random errors due to sparse data and repetitive testing of the accumulating data (Brok 2008; Wetterslev 2008; Brok 2009). To minimise random errors, we calculated the required information size (i.e., the number of participants needed in a meta-analysis to detect or reject a certain intervention effect) (Wetterslev 2008). The required information size calculation should also account for the heterogeneity or diversity present in the meta-analysis (Wetterslev 2008; Wetterslev 2009). In our meta-analysis, the diversity-adjusted required information size was based on the event proportion in the control group; assumption of a plausible RR reduction of 20% or the RR reduction observed in the included trials with low risk of bias; a risk of type I error of 5%; a risk of type II error of 20%; and the assumed diversity of the meta-analysis (Wetterslev 2009). We added the trials according to the year of publication, and if more than one trial was published in a year, trials were added alphabetically according to the last name of the first author. On the basis of the required information size, trial sequential monitoring boundaries were constructed (Lan 1983; Wetterslev 2008; Thorlund 2011). These boundaries determine the statistical inference one may draw regarding the cumulative meta-analysis that has not reached the required information size; if the trial sequential monitoring boundary for benefit or harm is crossed before the required information size is reached, firm evidence may perhaps be established and further trials may turn out to be superfluous. On the other hand, if the boundary is not surpassed, it is most probably necessary to continue doing trials in order to detect or reject a certain intervention effect. This can be determined by assessing if the cumulative Z-curve crosses the trial sequential boundaries for futility. If futility boundaries are crossed, then further trials may be unnecessary (CTU 2011).

We conducted trial sequential analyses using software from The Copenhagen Trial Unit (CTU 2011).

Subgroup analysis and investigation of heterogeneity

Subgroup analyses were performed to compare the following.

- Trials with low risk compared to trials with high risk of bias.
- Type of patients regarding previous antivirals: naives, relapsers, and non-responders.
- Type of patients regarding genotype: genotype 1 compared to genotype non-1.

- Type of patients regarding degree of liver disease (inflammation score (grading) or fibrosis score (staging)).
- Type of patients regarding HIV or hepatitis B co-infection.
- Type of patients regarding age: children compared to adults.
- Intervention: according to the type, dose and duration of aminoadamantanes, and other viral drugs.

Subgroups were compared with test of interaction (Altman 2003).

Sensitivity analysis

Suitable sensitivity analyses were identified during the review process, e.g., a sensitivity analysis was used when imputing missing data with replacement values.

Data analysis in included trials: according to intention-to-treat principle as well as 'as treated' (per protocol) analysis.

'Summary of findings' table

We used the principles of the GRADE system to assess the quality of the body of evidence associated with all outcomes mentioned in our review and constructed 'Summary of findings' table using the GRADE software (ims.cochrane.org/revman/gradepro).

We assessed five factors referring to limitations in the study design and implementation of available studies suggesting high likelihood of bias; indirectness of evidence (population, intervention, control, outcomes); unexplained heterogeneity or inconsistency of results (including problems with subgroup analyses); imprecision of results (wide confidence intervals); and high probability of publication bias.

We defined the levels of evidence as:

- high-quality evidence when all bias domains were assessed with low risk of bias and there were consistent findings that were generalisable to most of the population of interest; there were sufficient data, with narrow confidence intervals; there were no known or suspected reporting biases; in such a case, "further research is very unlikely to change our confidence in the estimate of effect";
- moderate-quality evidence when "further research is likely to have an important impact on our confidence in the estimate of effect, and may change the estimate";

- low-quality evidence when the following statement applies: "further research is very likely to have an important impact on our confidence in the estimate of effect, and is likely to change the estimate";
- very low-quality evidence when the following statement applies: "we are very uncertain about
- the estimate".

Results

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

We identified 639 references through the electronic searches. After filtering for duplicates, 290 publications remained. Of the remaining 290 publications, 281 were excluded after screening the title and abstract, among others because they were reviews or because they did not describe a randomised clinical trial investigating the effect of aminoadamantanes in patients with chronic hepatitis C virus. The remaining nine references described six unique randomised clinical trials (Figure 1).

Two of these six included trials were published in more than one publication (Khalili 2000; Younossi 2001). All six trials were published in full paper articles (Khalili 2000; Younossi 2001; Bacosi 2002; Herrine 2005; Salmeron 2007; Abbas 2012).

When necessary, the primary or last authors were contacted for further information and data relating to the trials.
We did not identify any registered ongoing or planned trials when we searched the WHO International Clinical Trials Registry Platform (www.who.int/ictrp), Google Scholar, and Eudrapharm.

Included studies

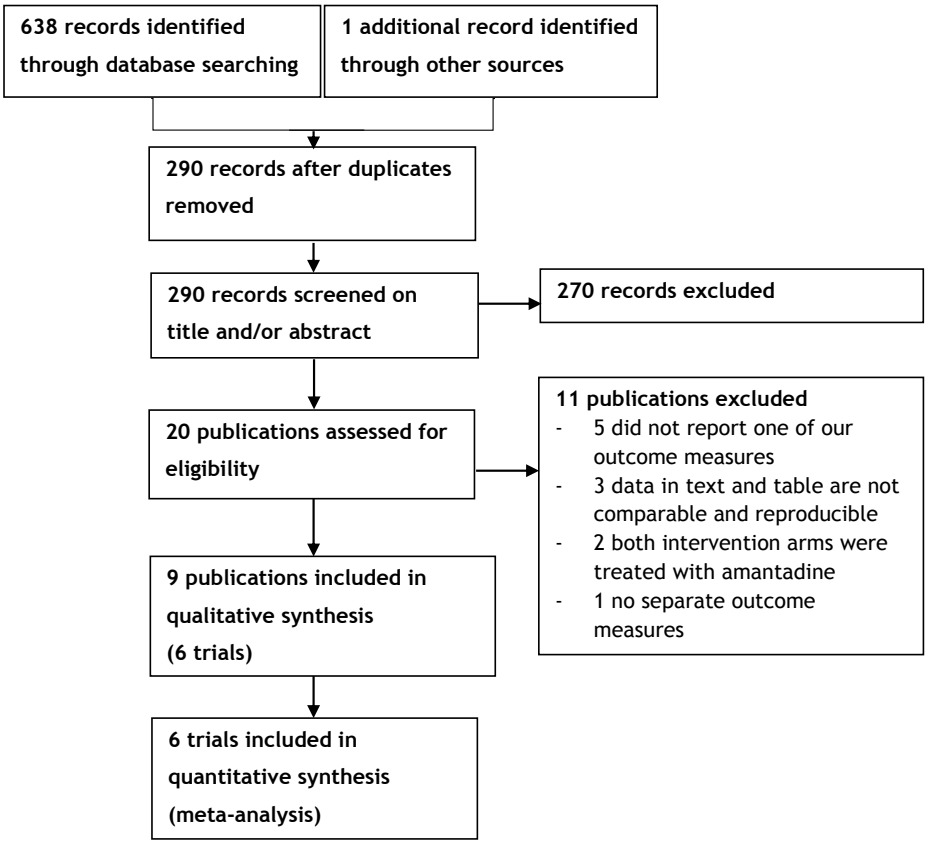
We included six trials in total. Three trials were conducted in the USA (Khalili 2000; Younossi 2001; Herrine 2005). The other three trials were conducted each in different countries: Italy

(Bacosi 2002), Pakistan (Abbas 2012), and Spain (Salmeron 2007) (see Characteristics of included studies).

The included trials were published from 2000 (Khalili 2000) to 2012 (Abbas 2012). Three trials had a parallel group design with two intervention groups (Khalili 2000; Younossi 2001; Abbas 2012). One

trial included three intervention groups (Bacosi 2002) and two trials included four intervention groups (Herrine 2005; Salmeron 2007).

Figure 1. Flow diagram



The six randomised clinical trials randomised 581 patients with chronic hepatitis C virus to amantadine versus control. The control arms consisted of ribavirin, mycophenolate mofetil, interferon-alpha, or interferon-gamma.

Three trials compared amantadine plus interferon-alpha versus ribavirin plus interferon-alpha (Khalili 2000; Younossi 2001; Salmeron 2007). One trial compared amantadine monotherapy with interferon-alpha without additional antiviral drugs (Bacosi 2002). One trial reported on amantadine plus interferon-alpha plus ribavirin versus interferon-gamma plus interferon-alpha plus ribavirin (Abbas 2012). Another trial compared amantadine plus peg interferon-alpha versus mycophenolate mofetil plus peg interferon-alpha (Herrine 2005). This trial also reported on the comparison of amantadine plus peg interferon-alpha versus ribavirin plus peg interferon-alpha (Herrine 2005).

Amantadine dose was the same in each trial, 200 mg daily. The treatment duration of the trials varied from six to 12 months. A six-month post-treatment duration of follow-up was used in all trials, except for one trial which applied 12 months of post-treatment follow-up (Bacosi 2002). The details are displayed in Table 1.

All publications reported the sex of the participants; more than 67% were men. All trials included adult patients. None of the trials included patients co-infected with HIV or hepatitis B virus infection.

Excluded studies

The eight excluded studies are listed under 'Characteristics of excluded studies', and the reasons for exclusion are given there.

Risk of bias in included studies

Risk of bias was assessed according to six domains: allocation sequence generation; allocation concealment; blinding of participants, personnel, and outcome assessors; handling of incomplete outcome data; selective outcome reporting; and for-profit bias. All included trials were considered to have high risk of bias. Our statistical analysis are, therefore, based on trials with a high risk of bias. For details of the judgements made for the individual trials, please see Figure 2 and Figure 3.

Allocation (selection bias)

The generation of the allocation sequence was adequately described in only one trial (Younossi 2001). The remaining five trials were described as randomised, but the method or performing random sequence generation was not described or the randomisation was done by the principle investigator (Characteristics of included studies).

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

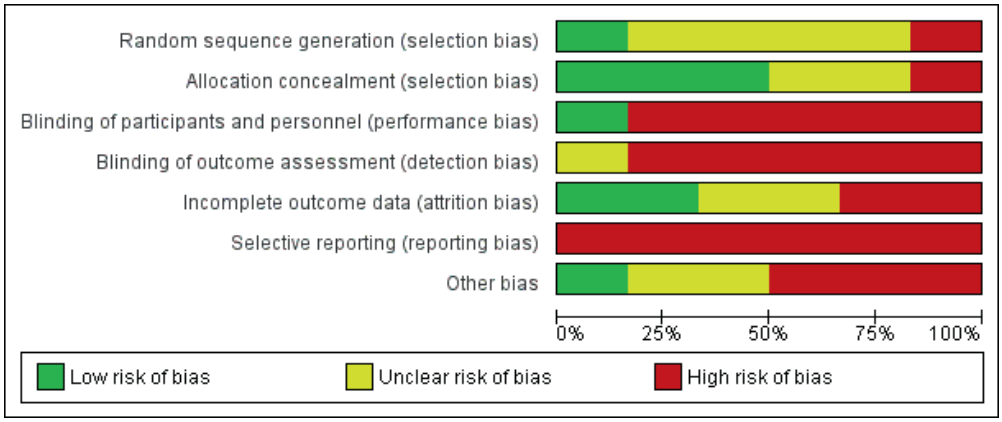
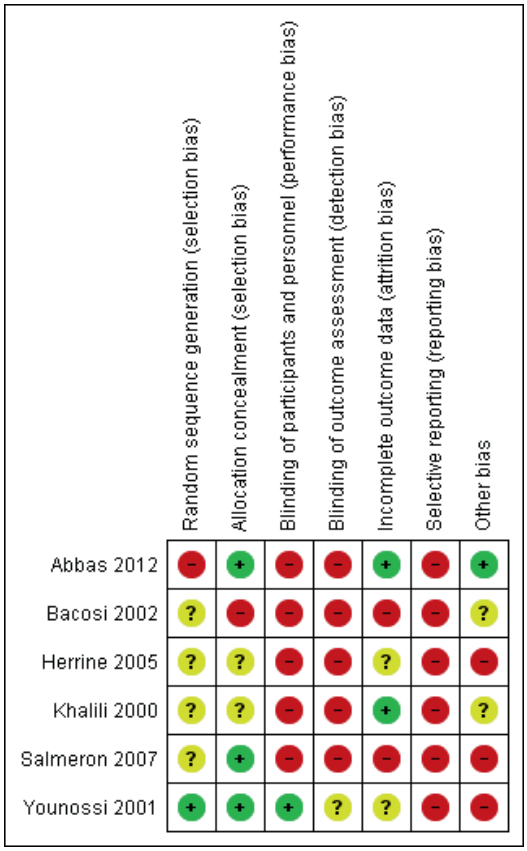


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



None of the trials adequately described the method of blinding of outcome assessment; thus, six trials were considered as high risk of bias (Characteristics of included studies). This also means that none of the included trials had a low risk of bias according to both blinding of participants and personnel and blinding of outcome assessments (Characteristics of included studies).

Incomplete outcome data (attrition bias)

Incomplete data were addressed adequately in two trials (Khalili 2000; Abbas 2012). In the other four trials, there

were risks of incomplete outcome data (Characteristics of included studies).

Selective reporting (reporting bias)

There were risks of selective reporting of outcomes in all six trials (Characteristics of included studies).

Other potential sources of bias

Only one trial did not receive funding or other for-profit support and was therefore of low risk of bias regarding for-profit domain (Abbas 2012). Three trials received funding from the medical industry (Younossi 2001; Herrine 2005; Salmeron 2007). It was unclear whether the remaining two trials received funding from the medical industry or other for-profit support (Khalili 2000; Bacosi 2002) (Characteristics of included studies). We considered these last five trials as having high risk of bias for the for-profit bias domain (Figure 3).

There were no baseline differences in any of the trials, except for one in which there was baseline imbalance regarding age (Khalili 2000). One trial stopped early due to poor results (Salmeron 2007).

Effects of interventions

See: Summary of findings for the main comparison

Amantadine versus ribavirin

Three trials compared amantadine plus interferon-alpha versus ribavirin plus interferon-alpha; one trial compared amantadine plus peg interferon-alpha versus ribavirin plus peg interferon-alpha.

Primary outcomes

The composite outcome of all-cause mortality or liver-related morbidity

Four trials provided information on all-cause mortality or liver-related morbidity. The combined outcome measure was zero in both the 216 participants in the amantadine group and the 211 patients in the ribavirin group (Analysis 1.1). We were not able to perform meta-analyses on these data in RevMan, but with trial sequential analysis and a continuity correction of 0.5, we found no significant differences (fixed-effect model: risk ratio (RR) 0.98; 95%

confidence interval (CI) 0.00 to 248.89). The required information size to detect or reject a relative risk reduction (RRR) of 20% with a between-trial heterogeneity of 0% is estimated to be 140,645 patients. The actually accrued number of patients was 427, which was only 0.3% of the required information size.

Adverse events

We classified adverse events into two groups: number of patients with serious adverse events and number of patients with treatment discontinuation due to any adverse event.

Ten patients of 216 (5%) in the amantadine group versus 18 patients of 211 patients (9%) in the ribavirin group were reported with either serious adverse events or treatment discontinuation due to any adverse event (Analysis 1.2). Meta-analyses showed no statistically significant difference (fixed-effect model: RR 0.56; 95% CI 0.27 to 1.16; I^2 = 20%) (Analysis 1.2).

As there were no trials with low risk of bias, we performed trial sequential analysis on all included trials reporting on adverse events. Trial sequential analysis of these data showed there was too little information to draw any firm conclusions (Figure 4).

Quality of life

Only one trial reported on quality of life (Younossi 2001). Health-related quality of life (HRQL) was assessed at baseline and every three months using the medical outcome study Short Form-36 (SF-36) and a validated liver disease-specific instrument, Chronic Liver Disease Questionnaire (CLDQ). We were not able to perform meta-analyses on quality of life due to a lack of valid data. Overall, we found no significant differences between treatment with amantadine versus ribavirin in this trial.

Secondary outcomes

Failure of serum (or plasma) sustained virological response

Four trials provided information on patients who failed to achieve a sustained virological response. In the amantadine group, 206 of 216 patients (95%) did not achieve sustained virological response versus 176 of 211 patients (83%) in the ribavirin group. Meta-analysis with the fixed-effect model showed an effect on failure to achieve sustained virological response favouring the ribavirin group: RR 1.14; 95% CI 1.07 to 1.22. This estimated RR with a random-

effects model was similar, with marginally wider confidence intervals including the null: RR 1.15; 95% CI 0.99 to 1.32; I^2 = 78%) (Analysis 1.3).

Three trials reported on failure to achieve sustained virological response in patients treated with amantadine plus interferon-alpha versus ribavirin plus interferon-alpha (Analysis 1.3). One-hundred and seventy-eight participants of 185 participants (96%) in the amantadine group versus 156 participants of 179 participants (87%) in the ribavirin group failed to achieve sustained virological response. This negative effect of amantadine plus interferon-alpha compared with ribavirin plus interferon-alpha, shown by the fixed-effect meta-analysis was not observed in the random-effects model analysis (fixed-effect model: RR 1.10; 95% CI 1.04 to 1.18; random-effects model: RR 1.09; 95% CI 0.98 to 1.21; I^2 = 78%) (Analysis 1.3).

Figure 4. Trial sequential analysis on serious adverse events or patients discontinuation treatment due to an adverse event

SAE or AE discontinuation DARIS Pc 11%, RRR 20%, a 5%, b 20%, D 0% in a Two-sided graph.

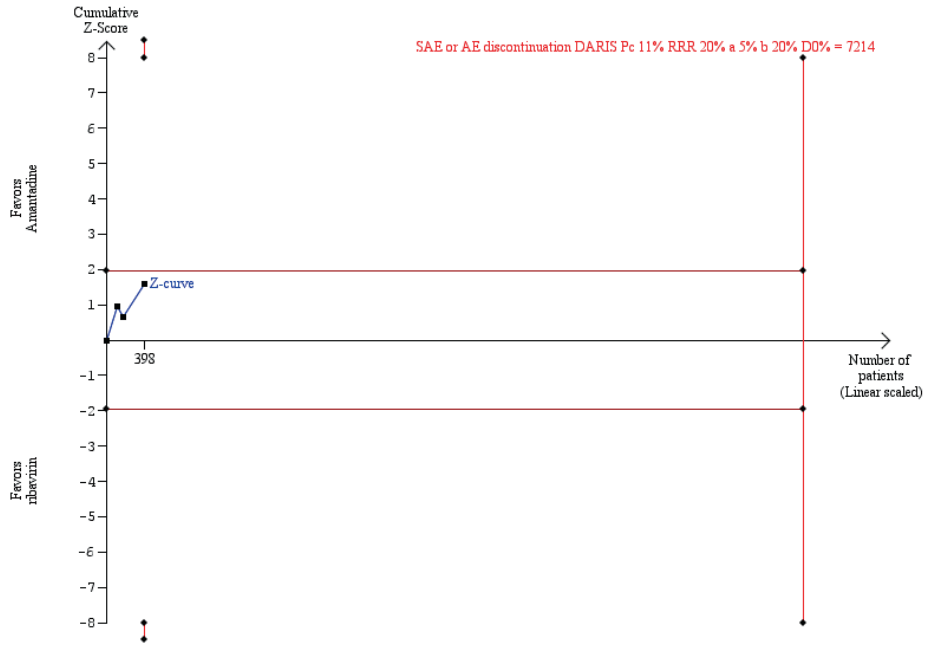


Figure 4: Trial sequential analysis of the random-effects meta-analysis of the effect of amantadine versus ribavirin in chronic hepatitis C-infected patients on number of patients experiencing a serious adverse event or number of patients who had to discontinue treatment due to an adverse event. The trial sequential analysis is performed with a type 1 error of 5% (two-sided), a power of 80%, an assumed control proportion of number of patients experiencing a serious adverse events or who had

to discontinue treatment due to an adverse event of 11%, and an anticipated relative risk reduction (RRR) of 20%. The diversity-adjusted required information size (DARIS) to detect or reject a RRR of 20% with a between-trial heterogeneity of 0% is estimated to be 7214 participants. The actually accrued number of participants is 398, which is only 6% of the DARIS. The blue cumulative Z-curve does not cross the red trial sequential monitoring boundaries for benefit or harm. Therefore, there is no evidence to support that amantadine influences number of patients experiencing a serious adverse event or who had to discontinue treatment due to an adverse event. The cumulative Z-curve does not reach the futility area (which is not even drawn by the program), demonstrating that further randomised trials may be needed.

Sixty-three patients were treated in one trial with amantadine plus peg interferon-alpha versus ribavirin plus peg interferon-alpha (Analysis 1.3). Twenty-eight of 31 participants (90%) treated in the amantadine group compared with 20 of 32 participants (63%) in the ribavirin group failed to achieve sustained virological response. Risk ratio for this event was statistically significant comparing amantadine plus peg interferon-alpha therapy with ribavirin plus peg interferon-alpha (fixed-effect model: RR 1.45; 95% CI 1.08 to 1.94) (Analysis 1.3).

Analysing the missing data as the *best-worst case scenario* in all the four trials comparing amantadine with ribavirin (assuming that participants with unknown status of achieving sustained virological response receiving amantadine did achieve sustained virological response, and that all participants from the ribavirin group with unknown status of achieving sustained virological response did not achieve sustained virological response) reveals no statistically significant differences in effect of amantadine versus ribavirin (fixed-effect model: RR 0.94; 95% CI 0.86 to 1.03; 427 participants, four trials). Analysing the missing data as the *worst-best case scenario* (assuming that participants with unknown status of achieving sustained virological response receiving amantadine did not achieve sustained virological response and that all participants from ribavirin group with unknown status of achieving sustained virological response achieved sustained virological response) shows an effect favouring ribavirin (fixed-effect model: RR 1.58; 95% CI 1.41 to 1.77; 427 participants, four trials).

We performed trial sequential analysis on all the trials. The trial sequential analysis of the combined data supports the finding that ribavirin is superior to amantadine with less failure to achieve sustained virological response (Figure 5). The result of the trial sequential analysis is shown by the cumulated Z-curve (blue curve) which crosses the trial sequential boundary (red inward sloping curve).

Figure 5. Trial sequential analysis on failure to achieve sustained virological response
Failure SVR DARIS PC 83%, RRR 20%, a 5%, b 20%, D 78% in a Two-sided graph.

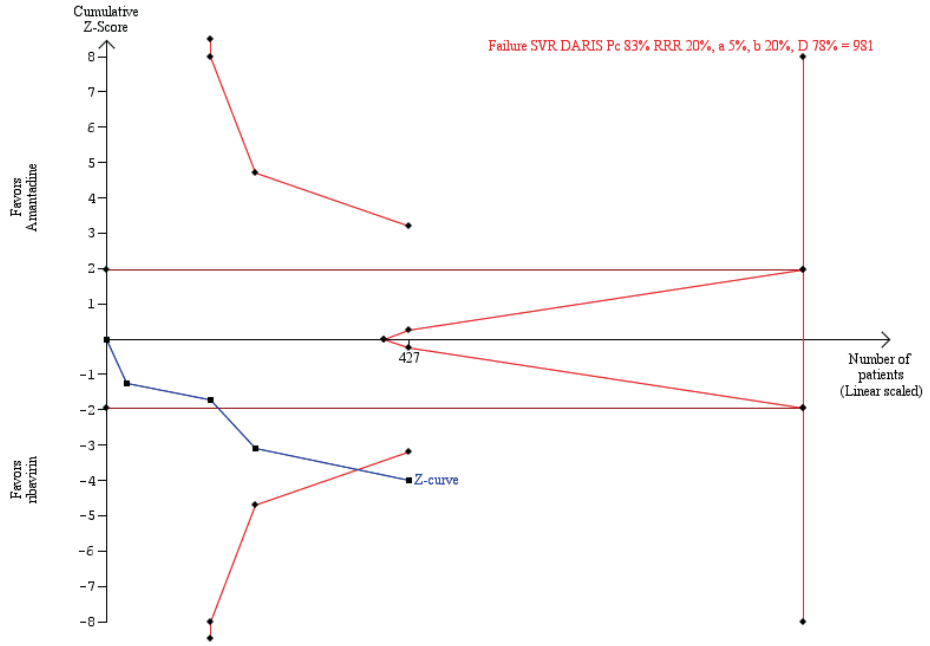


Figure 5: Trial sequential analysis of the random-effects meta-analysis of the effect of amantadine versus ribavirin on number of patients with chronic hepatitis C virus infection who failed to achieve a sustained virological response (SVR). The trial sequential analysis is performed with a type 1 error of 5% (two-sided), a power of 80%, an assumed control proportion of number of patients who failed to achieve an SVR of 83%, and an anticipated relative risk reduction (RRR) of 20%. The diversity-adjusted required information size (DARIS) to detect or reject a RRR of 20% with a between-trial heterogeneity of 78% is estimated to be 981 participants. The actually accrued number of participants is 427, which is 44% of the DARIS. The blue cumulative Z-curve crosses the red trial sequential monitoring boundary for harm. Therefore, there is evidence to support that ribavirin is superior compared with amantadine.

Failure of end-of treatment virological response

Three trials provided data on participants who failed to achieve end-of treatment virological response and could be included in the analyses (Analysis 1.4). In the amantadine group, 128 of 157 participants (82%) did not achieve end-of treatment virological response versus 103 of 152 participants (68%) in the ribavirin group. Meta-analysis showed that amantadine showed more failure to achieve end-of treatment virological response compared to ribavirin (fixed-effect model: RR 1.20; 95% CI 1.05 to 1.36; I^2 = 32%) (Analysis 1.4).

We performed trial sequential analysis on all the three trials. There is no evidence to support that amantadine influences the number of participants who failed to achieve an end-of treatment virological response (Figure 6).

Figure 6. Trial sequential analysis end-of treatment virological response

Failure end-of treatment virological response DARIS Pc 68%, RRR 20%, a 5%, b 20%, D 32% in a Two-sided graph.

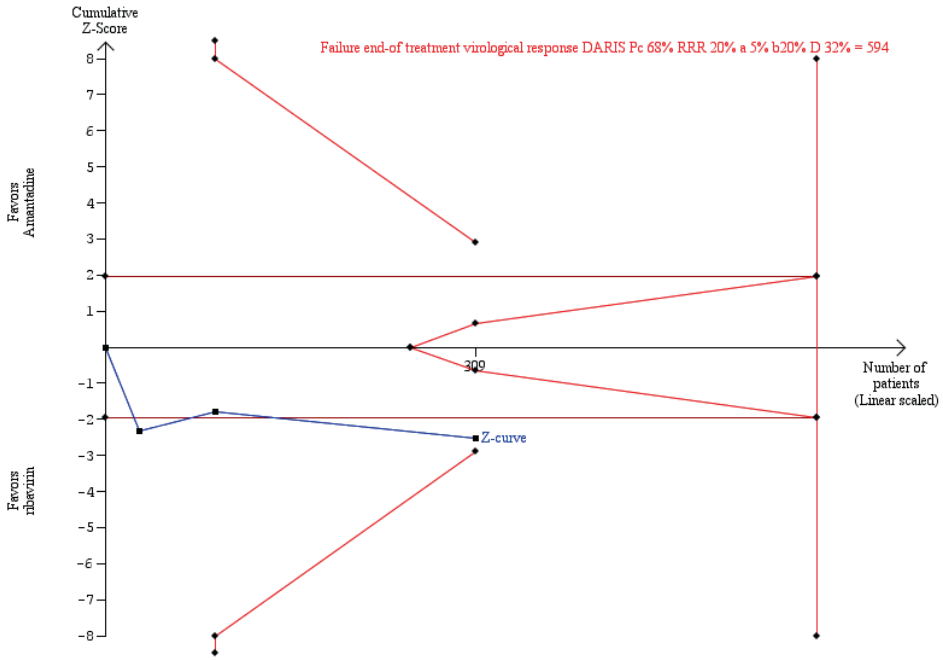


Figure 6: Trial sequential analysis of the random-effects meta-analysis of the effect of amantadine versus ribavirin on number of patients with chronic hepatitis C virus infection who failed to achieve an end-of treatment virological response. The trial sequential analysis is performed with a type 1 error of 5% (two-sided), a power of 80%, an assumed control proportion of number of patients who failed to achieve an SVR of 68%, and an anticipated relative risk reduction (RRR) of 20%. The diversity-adjusted required information size (DARIS) to detect or reject a RRR of 20% with a between-trial heterogeneity of 32% is estimated to be 594 participants. The actually accrued number of participants is 309, which is 52% of the DARIS. The blue cumulative Z-curve does not cross the red trial sequential monitoring boundaries for benefit or harm. Therefore, we cannot exclude random error.

Analysing the data in the best-worst case scenario regarding missing data (assuming that participants with unknown status of achieving end-of treatment virological response receiving amantadine did achieve end-of treatment virological response, and that all participants from

the ribavirin group with unknown status of achieving end-of treatment virological response did not achieve end-of treatment virological response) reveals no differences in effect estimate; thus, no negative effect of amantadine (fixed-effect model: RR 0.91; 95% CI 0.78 to 1.07; 309 participants, three trials). Analysing the data in the worst-best case scenario regarding missing data (assuming that participants with unknown status of achieving end-of treatment virological response receiving amantadine did not achieve end-of treatment virological response, and that all participants from control group with unknown status of achieving end-of treatment virological response did achieve end-of treatment virological response) reveals a stronger effect favouring ribavirin (fixed-effect model: RR 2.01; 95% CI 1.64 to 2.46; 309 participants, three trials).

Failure in histological response

None of the included trials provided information on the number of participants without improvement of histology.

Failure of normalisation of serum ALT levels at end-of treatment and at end-of follow-up

All trials that reported on biochemical response, only reported on ALT levels.

Only one trial provided information on failure of normalisation of end-of treatment biochemical response. In the amantadine group, 13 of 15 participants (87%) did not achieve end-of treatment biochemical response versus 6 of 14 participants (43%) in the ribavirin group. Meta-analyses showed that amantadine resulted in more participants without normalisation of ALT serum levels at end-of treatment compared with ribavirin (fixed-effect model: RR 2.02; 95% CI 1.07 to 3.82) (Analysis 1.5).

In two trials, 41 participants of 46 participants (89%) treated with amantadine compared with 31 of 46 participants (67%) in the ribavirin group failed to achieve end-of follow-up biochemical response (Analysis 1.6). Meta-analysis (fixed-effect model; RR 1.31; 95% CI 1.05 to 1.63; I^2 = 12%) showed that amantadine more often failed to achieve end-of follow-up biochemical response compared to ribavirin (Analysis 1.6).

Amantadine versus mycophenolate mofetil

Only one trial provided information on the comparison amantadine versus mycophenolate mofetil (Herrine 2005). The included trial reported on 31 participants in the amantadine group versus 29 participants in the mycophenolate mofetil group.

The all-cause mortality or liver-related morbidity was zero in both intervention arms (Analysis 2.1).

Five participants of 31 (16%) in the amantadine group versus five participants of 29 participants (17%) in the mycophenolate mofetil group were reported with either serious adverse events or treatment discontinuation due to any adverse event (Analysis 2.2). There were no significant differences between the groups (fixed-effect model: RR 0.94; 95% CI 0.30 to 2.90) (Analysis 2.2). The required information size to detect or reject a RRR of 20% with a between-trial heterogeneity of 14% is estimated to be 4093 participants. The actually accrued number of participants is 60, which is only 1% of the required information size.

Twenty-eight participants (90%) failed to achieve sustained virological response in the amantadine group versus 24 participants (83%) in the mycophenolate mofetil group. There was no significant difference in effect (fixed-effect model: RR 1.09; 95% CI 0.89 to 1.34) (Analysis 2.3). The required information size to detect or reject a RRR of 20% with a between-trial heterogeneity of 87% is estimated to be 1661 participants. The actually accrued number of participants is 60, which is only 4% of the required information size.

There was a significant negative effect of amantadine on failure to achieve end-of treatment virological response (fixed-effect model: RR 2.10; 95% CI 1.09 to 4.08). In the amantadine group, 18 of 31 participants (58%) did not achieve end-of treatment virological response versus 8 of 29 participants (28%) in the mycophenolate mofetil group (Analysis 2.4). Trial sequential analysis showed a required information size of 4017 participants. The actually accrued number of participants is 60, which is only 1% of the required information size.

The included trial did not provide information on quality of life, histological response, and normalisation of ALT at end-of treatment.

Twenty-six participants treated with amantadine (84%) compared with 23 participants treated with mycophenolate mofetil (79%) failed to achieve end-of follow-up biochemical response (Analysis 2.5). Meta-analyses showed no statistically significant difference (fixed-effect model: RR 1.06; 95% CI 0.83 to 1.35) (Analysis 2.5).

Due to the limited number of participants, we were unable to perform any of the remaining planned sensitivity analysis or funnel plot analysis.

Amantadine versus interferon-alpha

One trial reported on the comparison amantadine versus interferon-alpha (Bacosi 2002). The included trial reported on 42 participants in the amantadine group versus 39 participants in the interferon-alpha group.

The included trial did not provide information on all-cause mortality, liver-related morbidity, quality of life, or histological response.

Zero participants of 42 (0%) in the amantadine group versus 3 participants of 39 participants (8%) in the interferon-alpha group were reported with either serious adverse events or treatment discontinuation due to any adverse event (Analysis 3.1). The required information size to detect or reject a RRR of 20% with a between-trial heterogeneity of 0% is estimated to be 8539 participants. The actually accrued number of participants is 81, which is only 1% of the required information size.

Thirty-five participants (83%) failed to achieve sustained virological response in the amantadine group versus 30 participants (77%) in the interferon-alpha group, which showed no significant difference in effect (fixed-effect model: RR 1.08; 95% CI 0.87 to 1.35) (Analysis 3.2). The required information size to detect or reject a RRR of 20% with a between-trial heterogeneity of 81% is estimated to be 1484 participants. The actually accrued number of participants is 81, which is only 5% of the required information size.

Regarding failure to achieve end-of treatment virological response, there were no significant differences in effect between amantadine and interferon-alpha (fixed-effect model: RR 1.25; 95% CI 0.96 to 1.62). In the amantadine group, 35 of 42 participants (83%) did not achieve end-of treatment virological response versus 26 of 39 participants (67%) in the interferon-alpha group (Analysis 3.3). Trial sequential analysis showed a required information size of 1745 participants. The actually accrued number of participants is 81, which is only 5% of the required information size.

In the amantadine group, 21 of 42 participants (50%) did not achieve end-of treatment biochemical response versus 22 of 39 participants (56%) in the interferon-alpha group. Meta-analyses showed no significant difference in the number of participants without normalisation of ALT serum levels at end-of treatment compared amantadine with interferon-alpha (fixed-

effect model: RR 0.89; 95% CI 0.59 to 1.33) (Analysis 3.4). Trial sequential analysis showed a required information size of 1252 participants. The actually accrued number of participants is 81, which is only 6% of the required information size.

Twenty-five participants (60%) treated with amantadine compared with 26 participants (67%) in the interferon-alpha group failed to achieve end-of follow-up biochemical response (Analysis 3.5). Meta-analyses showed no statistically significant difference (fixed-effect model: RR 0.89; 95% CI 0.64 to 1.25) (Analysis 3.5). Trial sequential analysis showed a required information size of 1074 participants. The actually accrued number of participants is 81, which is only 8% of the required information size.

Due to the limited number of participants, we were unable to perform any of the remaining sensitivity analysis, or funnel plot analysis.

Amantadine versus interferon-gamma

One trial provided information on the comparison amantadine versus interferon-gamma (Abbas 2012). This trial reported on 22 participants in both the amantadine group and the interferon-gamma group.

The all-cause mortality or liver-related morbidity was zero in both intervention arms (Analysis 4.1). The required information size to detect or reject a RRR of 20% with a between-trial heterogeneity of 0% is estimated to be 70,005 participants. The actually accrued number of participants is 44, which is only 0.06% of the required information size.

Two participants in the amantadine group (9%) versus zero participants (0%) in the interferon-gamma group were reported with either serious adverse events or treatment discontinuation due to any adverse event (Analysis 4.2). The required information size to detect or reject a RRR of 20% with a between-trial heterogeneity of 50% is estimated to be 140,010 participants. The actually accrued number of participants is 44, which is only 0.03% of the required information size.

Sixteen participants failed to achieve sustained virological response in the amantadine group versus 11 participants in the interferon-gamma group. There was no significant effect of amantadine compared with interferon-gamma (fixed-effect model: RR 1.45; 95% CI 0.89 to 2.37) (Analysis 4.3). The required information size to detect or reject a RRR of 20% with a between-trial heterogeneity of 66% is estimated to be 2288 participants. The actually accrued number of participants is 44, which is only 2% of the required information size.

Also, there was no significant effect of amantadine compared with interferon-gamma on failure to achieve end-of treatment virological response (fixed-effect model: RR 1.36; 95% CI 0.82 to 2.26). In the amantadine group, 15 participants (68%) did not achieve end-of treatment virological response versus 11 participants (50%) in the interferon-gamma group (Analysis 4.4). The required information size to detect or reject a RRR of 20% with a between-trial heterogeneity of 63% is estimated to be 2102 participants. The actually accrued number of participants is 44, which is only 2% of the required information size.

The included trial did not provide information on the outcome measures: quality of life and histological response.

In the amantadine group, 15 participants (68%) did not achieve end-of treatment biochemical response versus 11 participants (50%) in the interferon-gamma group. Meta-analyses showed no significant difference in effect comparing amantadine with interferon-gamma (fixed-effect model: RR 1.36; 95% CI 0.82 to 2.26) (Analysis 4.5). Again, trial sequential analysis showed a required information size of 2102 participants. The actually accrued number of participants is 44. This is only 2% of the required information size.

Sixteen participants (73%) treated with amantadine compared with 11 participants (50%) in the interferon-gamma group failed to achieve end-of follow-up biochemical response (Analysis 4.6). Meta-analyses showed no differences (fixed-effect model: RR 1.45; 95% CI 0.89 to 2.37) (Analysis 4.6). Trial sequential analysis showed a required information size of 2288 participants. The actually accrued number of participants is 44, which is only 2% of the required information size.

Due to the limited number of participants, we were unable to perform any of the remaining planned trial sequential analysis, sensitivity analysis, or funnel plot analysis.

Amantadine versus other antiviral-drugs

For completeness we have also meta-analysed data from all comparisons together in order to answer the question: which is best, amantadine or other antivirals? The heterogenous group of other antivirals seemed superior.

Summary of findings

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) 'Summary of findings' table (Guyatt 2008) is shown in Summary of findings for the main comparison.

Discussion

Summary of main results

We included six randomised clinical trials with 581 participants that assessed the benefits and harms of amantadine versus other antiviral drugs for the treatment of chronic hepatitis C virus. Amantadine was compared with four other antiviral drugs: ribavirin, mycophenolate mofetil, interferon-alpha, or interferon-gamma. The effect of amantadine was evaluated in four different treatment strategies: monotherapy of amantadine, combination therapy of amantadine with interferon-alpha, combination therapy of amantadine plus interferon-alpha and ribavirin, and combination therapy of amantadine plus peg interferon-alpha. All trials had high risks of bias.

This systematic review did not show any benefit of amantadine on all-cause mortality or liver-related morbidity.

Furthermore, our systematic review also showed that amantadine for participants with chronic hepatitis C virus is not associated with an increase or a reduction of adverse events, defined by the number of participants who experienced a serious adverse event or who had to discontinue treatment due to an adverse event. These results are confirmed by trial sequential analyses.

When comparing amantadine versus ribavirin, amantadine seems inferior as the proportion of participants who failed to achieve sustained virological response was larger in the amantadine group. This finding was confirmed by a trial sequential analysis. However, when comparing amantadine with the other three antiviral drugs, we did not demonstrate that participants treated with amantadine had more failure in achieving sustained virological response. These findings could be due to type II errors or bias. Moreover, amantadine did not show to have decreased the overall proportion of participants who failed to achieve end-of treatment virological response. Again, type II errors or bias should be considered.

Unfortunately, we were not able to identify any benefits of amantadine on quality of life and histology because none of the included trials reported on quality of life or failure of histological improvement. We found a disadvantage of amantadine compared with ribavirin on biochemical end-of treatment and on end-of follow-up responses.

Overall completeness and applicability of evidence

This systematic review examined the evidence from six included randomised clinical trials for the use of treatment of hepatitis C virus. Despite efforts to obtain additional information from the trial authors, we could not obtain all relevant data, hence not all trials reported on all of our predefined outcomes.

Due to the limited number of included trials and participants, we were not able to perform subgroup analyses according to whether a patient had already received a previous antiviral therapy for hepatitis C virus, e.g., naive participants, relapsers, or non-responders, and if so, which treatment he/she had received. Five trials reported adequately on all-cause mortality or liver-related morbidity, and all six trials reported on serious adverse events and treatment discontinuation due to an adverse event. None of the included trials provided information on quality of life. Six trials reported on our first secondary outcome: failure of achieving sustained virological response. Five trials reported on failure of end-of treatment virological response. No trial provided information on failure in histological improvement, three trials reported on failure of biochemical response at end-of treatment, and four trials reported on failure of biochemical response at end-of follow-up.

It is questionable whether the included participants are representative for the current practice. All trials included participants with positive serum HCV RNA. However, there is heterogeneity among trials due to different disease severity of participants at entry, differences according to genotype (five trials included a mixture of genotypes), and differences regarding previous antiviral treatment. Concerning sex and age, the trials seem representative for current clinical care; more than 67% of the included participants were men and all trials included adult participants. None of the trials included participants with hepatitis B virus or HIV co-infection. Accordingly, we lack data on co-infected patients.

Quality of the evidence

We conducted this review according to *The Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and the Cochrane Hepato-Biliary Group Module (Gluud 2014). The

results of our meta-analysis, however, are only as strong as the quality of primary trials included.

The main limitation in the design and implementation is the lack of clarity of the generation of allocation sequence, concealment of allocation, and blinding. Of the included trials, only one (17%) reported adequate allocation sequence generation; only three (50%) adequately reported on allocation concealment; and none reported blinding. Two trials (33%) adequately addressed incomplete data, but none of the trials reported on all clinically relevant and reasonably expected outcomes. Also, one trial (17%) appeared to be free of other components that could put them at risk of bias. Accordingly, all trials were with high risk of bias. It is surprising to see that none of the trials were considered as having low risk of bias, in spite of the repeated calls for improved trial quality both within and outside hepatology (Schultz 1995; Gluud 1998; Kjaergard 1999; Needleman 1999; Kjaergard 2001; Wood 2008; Savović 2012). Also, other bias domains had high risk of bias. Patients, patient organisations, and other stakeholders do not get unbiased research before the several calls for unbiased clinical research is followed by physicians, regulatory authorities, and industry.

Regarding precision of our results, some outcomes of the included trials in our meta-analysis include few participants and few events, and thus the confidence intervals around the estimate of effect are large.

All trials measured sustained virological response which is currently the most commonly used surrogate outcome measure of benefit. Recent large cohort studies showed a positive correlation between the presence of viraemia and mortality (Butt 2009; Uto 2009). However, sustained virological response is still only a putative (unvalidated) surrogate outcome for the patient-relevant intervention effect of antivirals (Gluud 2007; Gurusamy 2013; Koretz 2013). Because randomised clinical trials need to inform clinical practice, clinical outcomes such as the risk of liver failure, hepatocellular carcinoma, mortality, and quality of life would be of greater interest to patients and clinicians. Such measures nevertheless require a follow-up of maybe up to five years. Currently, no randomised clinical trials assessing aminoadamantanes are of such long duration.

Potential biases in the review process

In this systematic review, a comprehensive literature search was performed. As far as we know, we have found all the evidence available. A potential limitation of our literature search may be that we have not specifically searched for trials in the grey literature which may have introduced a slight risk of bias into our meta-analysis (Egger 2003). However, the bias is

unlikely to influence our results in a beneficial way as trials found in grey literature rarely report beneficial effects (Hopewell 2007).

We only included six trials, in which four different antiviral regimens (ribavirin, mycophenolate mofetil, interferon-alpha, or interferon-gamma) were used as comparator drugs. Also, most of the included trials are of a relatively small size. This increases the risk of providing a more unrealistic estimate of the intervention effects due to bias (systematic errors) or chance (random errors) (Keus 2010). Risk of bias is known to have an impact on the estimated intervention effect, with trials with high risk of bias tending to overestimate beneficial intervention effects and underestimating harmful effects (Schultz 1995; Moher 1998; Kjaergard 2001; Wood 2008; Lundh 2012; Savović 2012; Savović 2012a). We could not divide the analysis for all outcomes into high risk of bias trials and low risk of bias trials to reveal any influence of bias on the effect estimates of our outcomes, because all six trials were considered to have high risk of bias.

No statistical signs of publication bias and other bias were observed.

This review meta-analysed data for all-cause mortality or liver-related morbidity from five trials involving 500 participants. We also meta-analysed data for serious adverse events or treatment discontinuation due to an adverse event from six trials involving 581 participants. The median length of trial duration was 12 months (two trials had a trial duration of six months), the median length of follow-up was six months (one trial had a follow-up of 12 months). For our primary outcome all-cause mortality or liver-related morbidity, this is not sufficiently long considering that the estimated median time in which hepatitis C virus progresses to cirrhosis is 15 years to 50 years (Koretz 1993; Kenny-Walsh 1999; Seeff 2009). Therefore, it is difficult to detect a significant difference on all-cause mortality and liver-related morbidity based on these trials. If aminoadamantanes should have an effect on morbidity and mortality, one prerequisite would be that it significantly affected virological load. However, we were unable to extract viral data to show that this was the case.

We used trial sequential analysis (CTU 2011; Thorlund 2011) to control the risk of random errors which is higher when data come from trials with small sample sizes (Wetterslev 2008). The trial sequential analysis on the outcome serious adverse events or treatment discontinuation due to an adverse event showed no significant effect estimate applying both the random-effects and fixed-effect models in participants treated with amantadine. The trial sequential analysis on the secondary outcome measure sustained virological response applied for amantadine compared with ribavirin demonstrated a negative effect on the number of

participants who failed to achieve sustained virological response in participants treated with amantadine. Thus, random errors seem to have been excluded for this comparison, but systematic errors may remain.

Heterogeneity among trials might be due to differences in dose, duration and type of interferon-alpha, or peg interferon-alpha. The inclusion of interferon-alpha as well as peg interferon-alpha with pharmacokinetic differences might have influenced the observed outcomes and comparability of results with earlier publications. Also, different definitions of non-responders were used, such as non-responder to previous interferon-alpha therapy alone or non-responder to combination therapy of interferon-alpha with ribavirin. Furthermore, there could be heterogeneity among trials due to disease severity of participants at entry and differences according to genotype, both of which can affect the sustained virological response rates. To reflect our concern about heterogeneity, we conducted all analyses using both the fixed-effect model and random-effects model. We only presented the results of the fixed-effect model if the results of the two models did not differ. Subgroup analyses of the pre-defined covariates trial risk of bias, genotype distribution, previous antiviral treatment, and degree of liver disease could not be performed because of the lack of trials that reported on these variables.

Agreements and disagreements with other studies or reviews

Less than about 10% of all hepatitis C virus infected patients will develop end-stage liver disease. Overall, we found that amantadine did not show any benefit on all-cause mortality or liver-related morbidity. Most trials report on the surrogate outcome sustained virological response, but as already mentioned, we do not know if sustained virological response results in less mortality or morbidity (Gluud 2007; Brok 2009; Gurusamy 2013; Koretz 2013; Hauser 2014; Hauser 2014a).

Also, considering failure in achieving sustained virological response, we found that amantadine did not show any benefit. On the contrary, amantadine showed less effect compared with ribavirin, a finding which was supported by the trial sequential analyses. This result is in accordance with the main findings of a published meta-analysis (Chen 2012) which suggests that there is no beneficial effect of adding amantadine to peg interferon-alpha plus ribavirin in naive hepatitis C virus genotype 1 patients. Our findings are contrary to the main findings of another meta-analyses (Deltenre 2004) which suggested a role for amantadine in non-responder patients. Furthermore, our results are also in contrast with another review

which suggests that there may be a limited role for combination therapy in naive patients (Lim 2005).

We have no evidence from randomised trials on long-term (> one year) effects of amantadine on our primary outcomes. Long-term effects would in particular be relevant for outcomes like all-cause mortality or liver-related morbidity.

Amantadine was generally well tolerated. We observed that amantadine was associated with non-serious adverse events and almost all trials reported in general similar frequencies and severities of adverse events in both amantadine groups versus control groups. This result is in accordance with a Cochrane review about amantadine and rimantadine for influenza A in children and the elderly (Alves Galvao 2012). This result is also somewhat comparable to two other Cochrane reviews. The review on amantadine and rimantadine in influenza A in adults showed significantly more adverse effects in patients receiving amantadine compared to placebo, but no increased risk of serious adverse events (Jefferson 2012). The second review reported on amantadine in Parkinson's disease and found that there is not enough evidence from trials about the effects of amantadine for people with Parkinson's disease, and that adverse events in trials so far have not been severe (Crosby 2009). In our analysis, amantadine was administered with interferon-alpha or peg interferon-alpha with or without ribavirin, except for one trial. Interferon-alpha-based therapy is typically associated with haematologic complications (i.e., neutropenia, thrombocytopenia), neuropsychiatric complications (i.e., memory and concentration loss, visual disturbances, headaches, depression, irritability), flu-like symptoms, hormonal complications (i.e., hypothyroidism, hyperthyroidism), gastrointestinal complications (i.e., nausea, vomiting, weight loss), and dermatologic complications (i.e., eczema, alopecia). The most well-known adverse effect of ribavirin is a dose-dependent haemolytic anaemia, but gastrointestinal adverse effects such as nausea are also reported (Chutaputti 2000; Soza 2002; Sulkowski 2004). In conclusion, both interferon-alpha and ribavirin have a variety and severity of adverse events, which may make it hard to detect less severe adverse events of amantadine. We cannot exclude less severe adverse events from amantadine, for example gastro-intestinal symptoms and insomnia.

Regarding tolerance of amantadine, we have to take into consideration the doses of amantadine. All included trials used an amantadine dose of 200 mg per day. One randomised trial that evaluated the safety and toxicity of amantadine in patients with chronic hepatitis C virus also investigated the maximum tolerable dose of amantadine (Smith 2004a). They reported an increase in biochemical response with higher daily doses of amantadine from 200 mg per day up to 500 mg per day in monotherapy. However, no statistically difference was

found in ALT values between those receiving 300 mg of amantadine or those receiving higher doses of amantadine. Also, increasing the amantadine dose did not result in more patients achieving sustained virological response comparing 200 mg per day with 300 mg to 500 mg per day (Smith 2004a).

Authors' conclusions

Implications for practice

This review shows that there seems to be no significant benefit of amantadine on hepatitis C virus-infected patients for all-cause mortality or liver-related morbidity, or on adverse events in hepatitis C-infected patients; although the timeframe for measuring the composite outcome was insufficient in the included randomised clinical trials. Furthermore, amantadine did not decrease the proportion of patients with failure to achieve sustained virological response compared with ribavirin. In the absence of convincing evidence of benefit, the use of amantadine seems only justified in the context of randomised clinical trials assessing the effects of combination therapy with peg interferon-alpha and ribavirin. We found no randomised clinical trials assessing other aminoadamantanes.

Implications for research

Given the results of our analysis, we cannot conclude whether new randomised clinical trials will or will not find any beneficial effect of amantadine on patients' survival in chronic hepatitis C patients. We found no evidence for other aminoadamantanes. Based on the results of the overall evidence, it appears less likely that future trials assessing amantadine or potentially other aminoadamantanes for patients with chronic hepatitis C would show strong benefits. Therefore, it is probably better to focus on the assessments of other direct acting antiviral drugs. To our knowledge, no ongoing trials investigate the effects of amantadine in hepatitis C-infected patients. Any further trials ought to be conducted and reported according to the SPIRIT and CONSORT guidelines (Schulz 2012).

Acknowledgements

We thank Dimitrinka Nikolova, Bianca Hemmingsen, Maria Skoog, Jane Lindschou, and Luit Penninga from The Cochrane Hepato-Biliary Group and The Copenhagen Trial Unit for helpful

discussions and comments. Furthermore, we thank Sarah Louise Klingenberg from The Cochrane Hepato-Biliary Group for helping developing the searches strategies and running the searches. We also thank the peer reviewers for their contribution to the protocol.

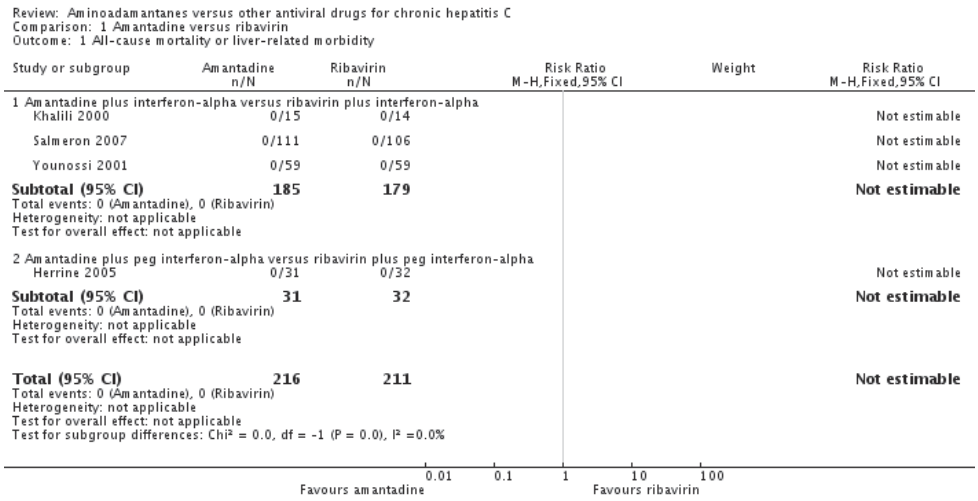
Peer reviewers: Sarah Louise Klingenberg, Denmark; Jane Lindschou, Denmark.
Contact editor: Janus Christian Jakobsen, Denmark.

Data and analyses

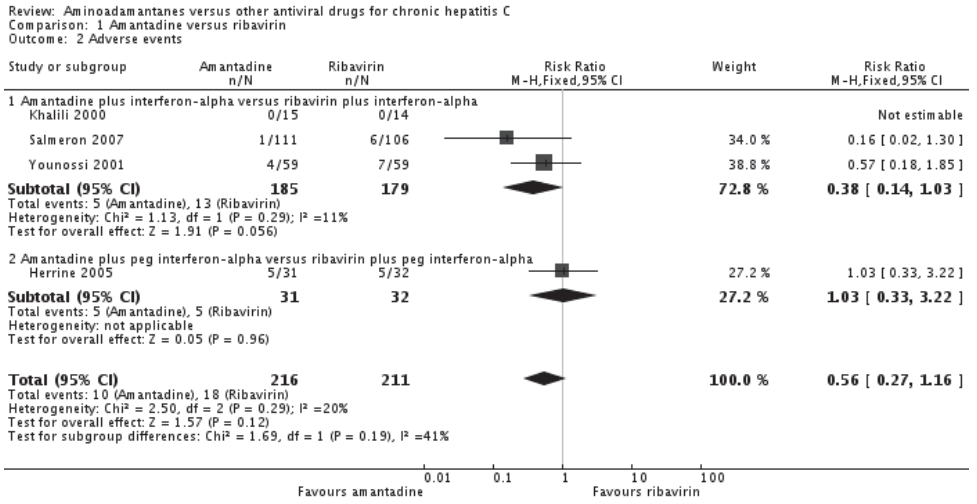
Comparison 1. Amantadine versus ribavirin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality or liver-related morbidity	4	427	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.1 Amantadine plus interferon-alpha versus ribavirin plus interferon-alpha	3	364	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Amantadine plus peg interferon-alpha versus ribavirin plus peg interferon-alpha	1	63	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Adverse events	4	427	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.27, 1.16]
2.1 Amantadine plus interferon-alpha versus ribavirin plus interferon-alpha	3	364	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.14, 1.03]
2.2 Amantadine plus peg interferon-alpha versus ribavirin plus peg interferon-alpha	1	63	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.33, 3.22]
3 Failure of sustained virological response	4	427	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [1.07, 1.22]
3.1 Amantadine plus interferon-alpha versus ribavirin plus interferon-alpha	3	364	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [1.04, 1.18]
3.2 Amantadine plus peg interferon-alpha versus ribavirin plus peg interferon-alpha	1	63	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [1.08, 1.94]
4 Failure of end of treatment virological response	3	309	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [1.05, 1.36]
4.1 Amantadine plus interferon-alpha versus ribavirin plus interferon-alpha	2	246	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [1.03, 1.32]
4.2 Amantadine plus peg interferon-alpha versus ribavirin plus peg interferon-alpha	1	63	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.85, 2.39]
5 Failure of normalisation of ALT at end of treatment	1	29	Risk Ratio (M-H, Fixed, 95% CI)	2.02 [1.07, 3.82]
5.1 Amantadine plus interferon-alpha versus ribavirin plus interferon-alpha	1	29	Risk Ratio (M-H, Fixed, 95% CI)	2.02 [1.07, 3.82]
6 Failure of normalisation of ALT at end of follow-up	2	92	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [1.05, 1.63]
6.1 Amantadine plus interferon-alpha versus ribavirin plus interferon-alpha	1	29	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.91, 1.48]
6.2 Amantadine plus peg interferon-alpha versus ribavirin plus peg interferon-alpha	1	63	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [1.02, 1.96]

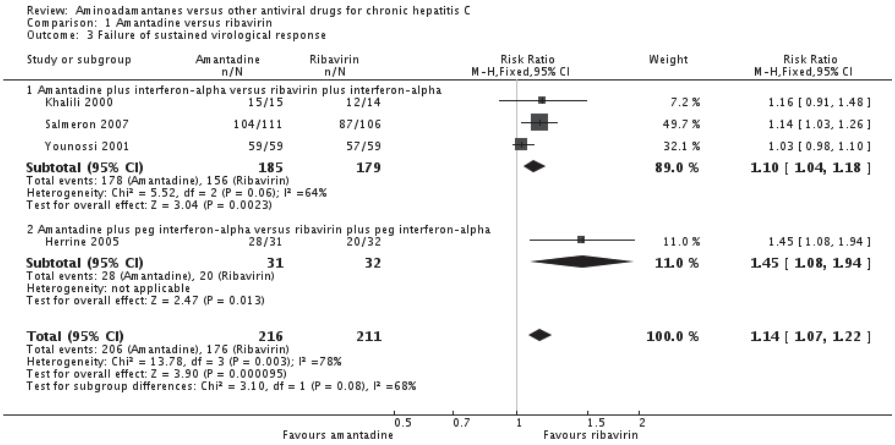
Analysis 1.1. Comparison 1 Amantadine versus ribavirin, Outcome 1 All-cause mortality or liver-related morbidity.



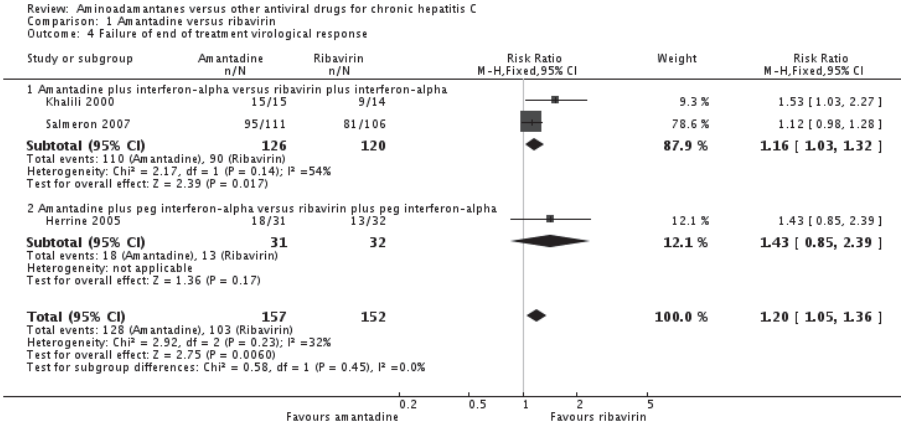
Analysis 1.2. Comparison 1 Amantadine versus ribavirin, Outcome 2 Adverse events.



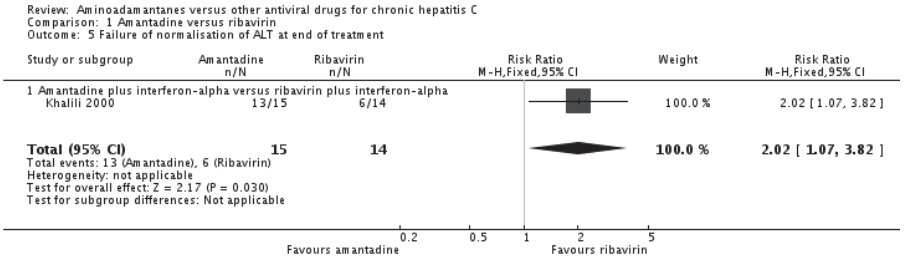
Analysis 1.3. Comparison 1 Amantadine versus ribavirin, Outcome 3 Failure of sustained virological response.



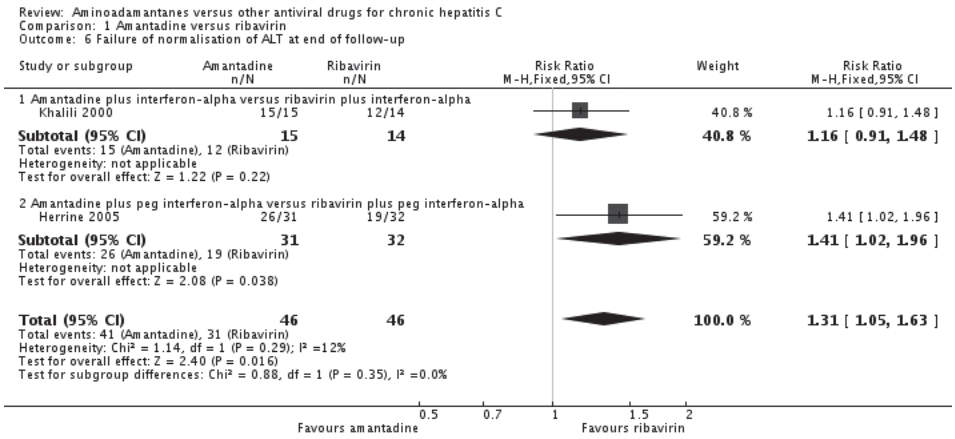
Analysis 1.4. Comparison 1 Amantadine versus ribavirin, Outcome 4 Failure of end of treatment virological response.



Analysis 1.5. Comparison 1 Amantadine versus ribavirin, Outcome 5 Failure of normalisation of ALT at end of treatment.



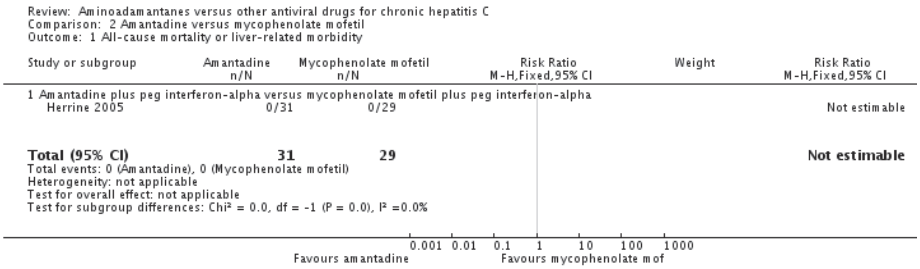
Analysis 1.6. Comparison 1 Amantadine versus ribavirin, Outcome 6 Failure of normalisation of ALT at end of follow-up.



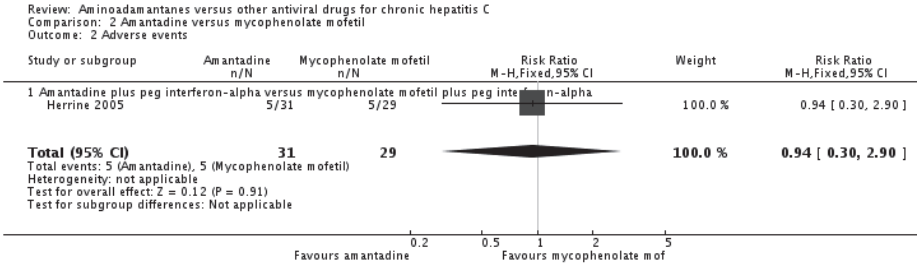
Comparison 2. Amantadine versus mycophenolate mofetil

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality or liver-related morbidity	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.1 Amantadine plus peg interferon-alpha versus mycophenolate mofetil plus peg interferon-alpha	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Adverse events	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.30, 2.90]
2.1 Amantadine plus peg interferon-alpha versus mycophenolate mofetil plus peg interferon-alpha	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.30, 2.90]
3 Failure of sustained virological response	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.89, 1.34]
3.1 Amantadine plus peg interferon-alpha versus mycophenolate mofetil plus peg interferon-alpha	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.89, 1.34]
4 Failure of end of treatment virological response	1	60	Risk Ratio (M-H, Fixed, 95% CI)	2.10 [1.09, 4.08]
4.1 Amantadine plus peg interferon-alpha versus mycophenolate mofetil plus peg interferon-alpha	1	60	Risk Ratio (M-H, Fixed, 95% CI)	2.10 [1.09, 4.08]
5 Failure of normalisation of ALT at end of follow-up	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.83, 1.35]
5.1 Amantadine plus peg interferon-alpha versus mycophenolate mofetil plus peg interferon-alpha	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.83, 1.35]

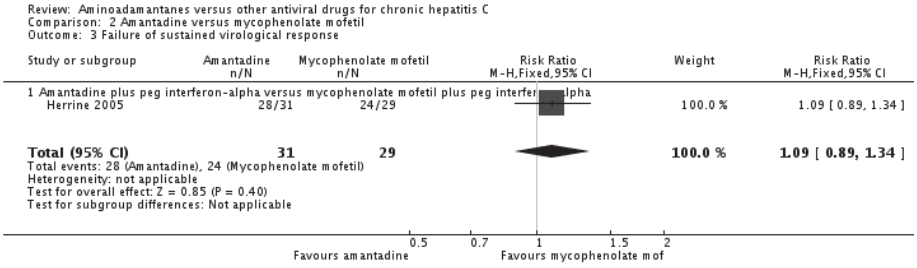
Analysis 2.1. Comparison 2 Amantadine versus mycophenolate mofetil, Outcome 1 All-cause mortality or liver-related morbidity.



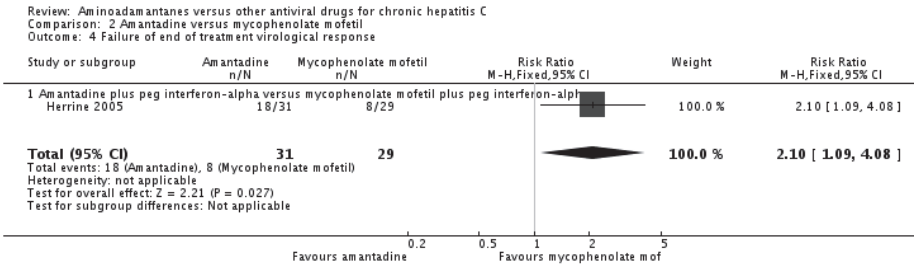
Analysis 2.2. Comparison 2 Amantadine versus mycophenolate mofetil, Outcome 2 Adverse events.



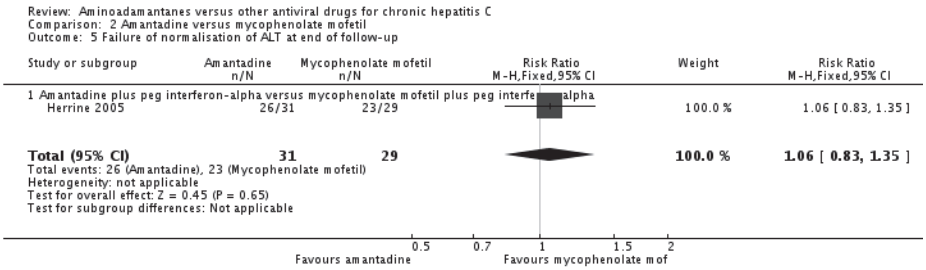
Analysis 2.3. Comparison 2 Amantadine versus mycophenolate mofetil, Outcome 3 Failure of sustained virological response.



Analysis 2.4. Comparison 2 Amantadine versus mycophenolate mofetil, Outcome 4 Failure of end of treatment virological response.



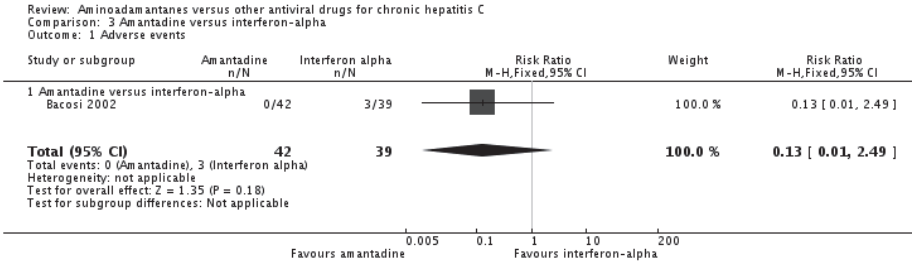
Analysis 2.5. Comparison 2 Amantadine versus mycophenolate mofetil, Outcome 5 Failure of normalisation of ALT at end of follow-up.



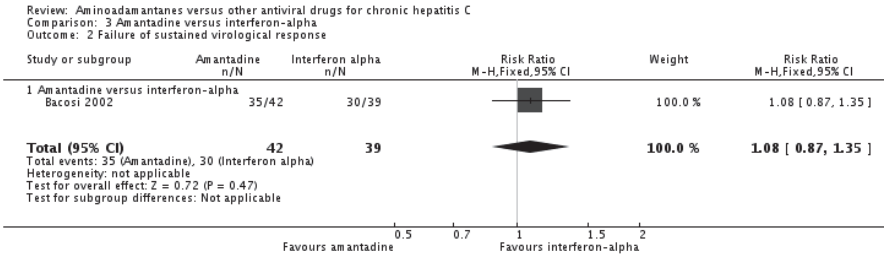
Comparison 3. Amantadine versus interferon-alpha

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse events	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.13 [0.01, 2.49]
1.1 Amantadine versus interferon-alpha	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.13 [0.01, 2.49]
2 Failure of sustained virological response	1	81	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.87, 1.35]
2.1 Amantadine versus interferon-alpha	1	81	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.87, 1.35]
3 Failure of end of treatment virological response	1	81	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.96, 1.62]
3.1 Amantadine versus interferon-alpha	1	81	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.96, 1.62]
4 Failure of normalisation of ALT at end of treatment	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.59, 1.33]
4.1 Amantadine versus interferon-alpha	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.59, 1.33]
5 Failure of normalisation of ALT at end of follow-up	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.64, 1.25]
5.1 Amantadine versus interferon-alpha	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.64, 1.25]

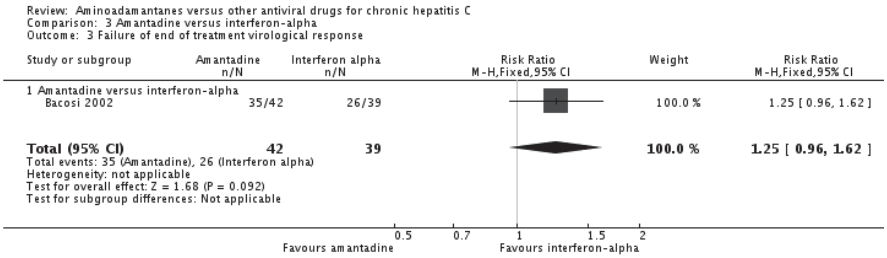
Analysis 3.1. Comparison 3 Amantadine versus interferon-alpha, Outcome 1 Adverse events.



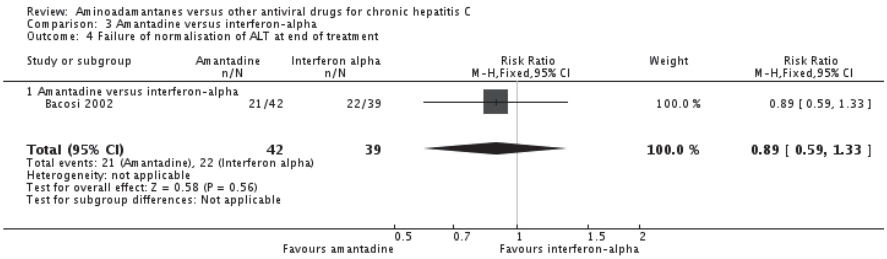
Analysis 3.2. Comparison 3 Amantadine versus interferon-alpha, Outcome 2 Failure of sustained virological response.



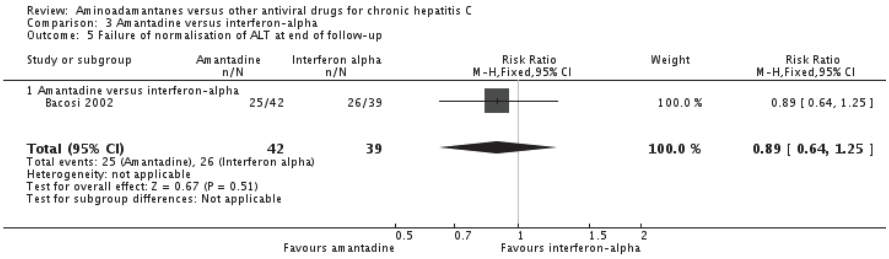
Analysis 3.3. Comparison 3 Amantadine versus interferon-alpha, Outcome 3 Failure of end of treatment virological response.



Analysis 3.4. Comparison 3 Amantadine versus interferon-alpha, Outcome 4 Failure of normalisation of ALT at end of treatment.



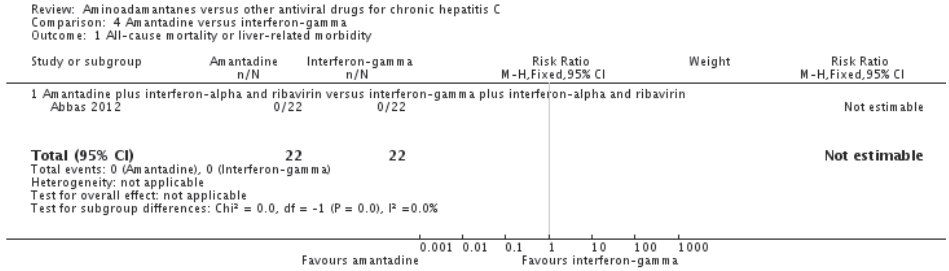
Analysis 3.5. Comparison 3 Amantadine versus interferon-alpha, Outcome 5 Failure of normalisation of ALT at end of follow-up.



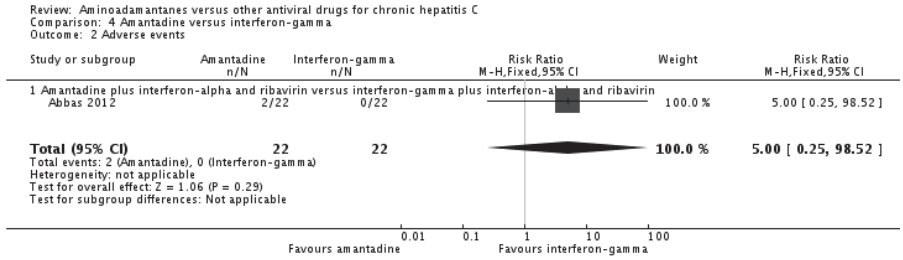
Comparison 4. Amantadine versus interferon-gamma

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality or liver-related morbidity	1	44	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.1 Amantadine plus interferon-alpha and ribavirin versus interferon-gamma plus interferon-alpha and ribavirin	1	44	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Adverse events	1	44	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.25, 98.52]
2.1 Amantadine plus interferon-alpha and ribavirin versus interferon-gamma plus interferon-alpha and ribavirin	1	44	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.25, 98.52]
3 Failure of sustained virological response	1	44	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [0.89, 2.37]
3.1 Amantadine plus interferon-alpha and ribavirin versus interferon-gamma plus interferon-alpha and ribavirin	1	44	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [0.89, 2.37]
4 Failure of end of treatment virological response	1	44	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [0.82, 2.26]
4.1 Amantadine plus interferon-alpha and ribavirin versus interferon-gamma plus interferon-alpha and ribavirin	1	44	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [0.82, 2.26]
5 Failure of normalisation of ALT at end of treatment	1	44	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [0.82, 2.26]
5.1 Amantadine plus interferon-alpha and ribavirin versus interferon-gamma plus interferon-alpha and ribavirin	1	44	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [0.82, 2.26]
6 Failure of normalisation of ALT at end of follow-up	1	44	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [0.89, 2.37]
6.1 Amantadine plus interferon-alpha and ribavirin versus interferon-gamma plus interferon-alpha and ribavirin	1	44	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [0.89, 2.37]

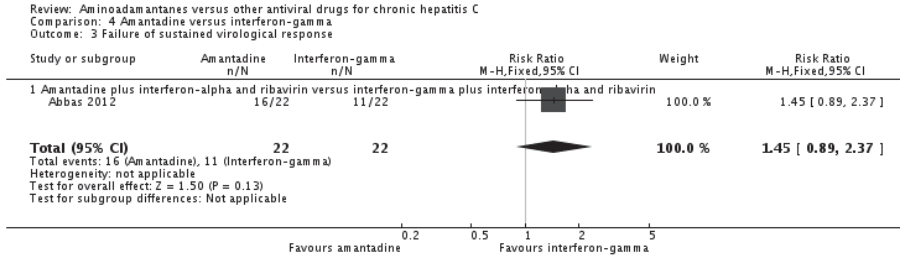
Analysis 4.1. Comparison 4 Amantadine versus interferon-gamma, Outcome 1 All-cause mortality or liver-related morbidity.



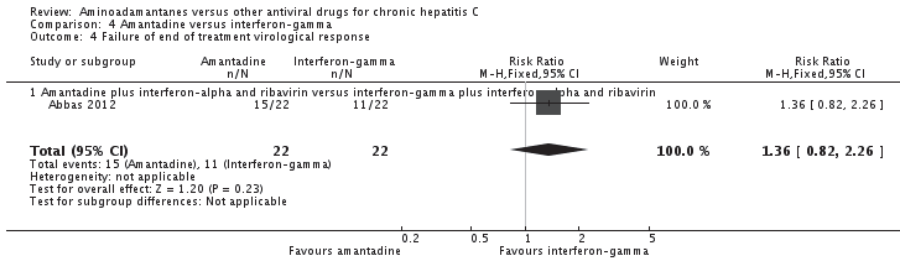
Analysis 4.2. Comparison 4 Amantadine versus interferon-gamma, Outcome 2 Adverse events.



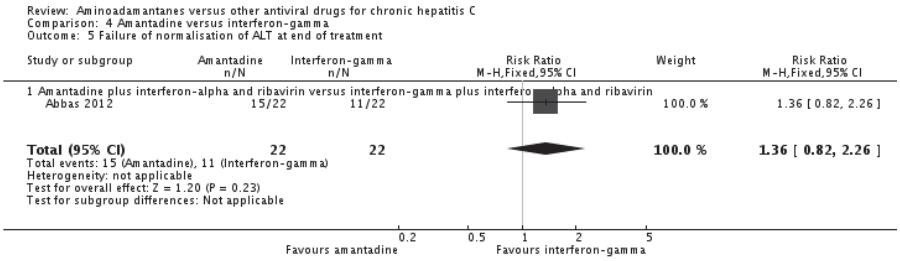
Analysis 4.3. Comparison 4 Amantadine versus interferon-gamma, Outcome 3 Failure of sustained virological response.



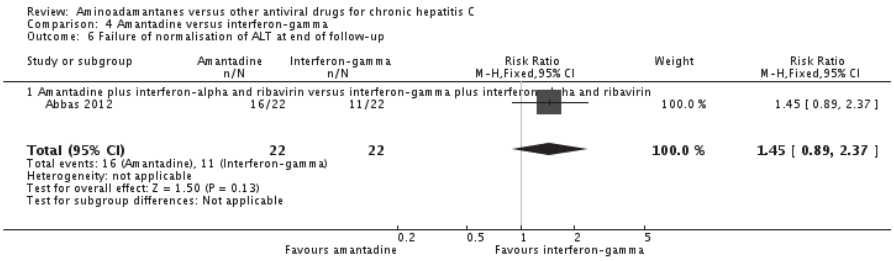
Analysis 4.4. Comparison 4 Amantadine versus interferon-gamma, Outcome 4 Failure of end of treatment virological response.



Analysis 4.5. Comparison 4 Amantadine versus interferon-gamma, Outcome 5 Failure of normalisation of ALT at end of treatment.



Analysis 4.6. Comparison 4 Amantadine versus interferon-gamma, Outcome 6 Failure of normalisation of ALT at end of follow-up.



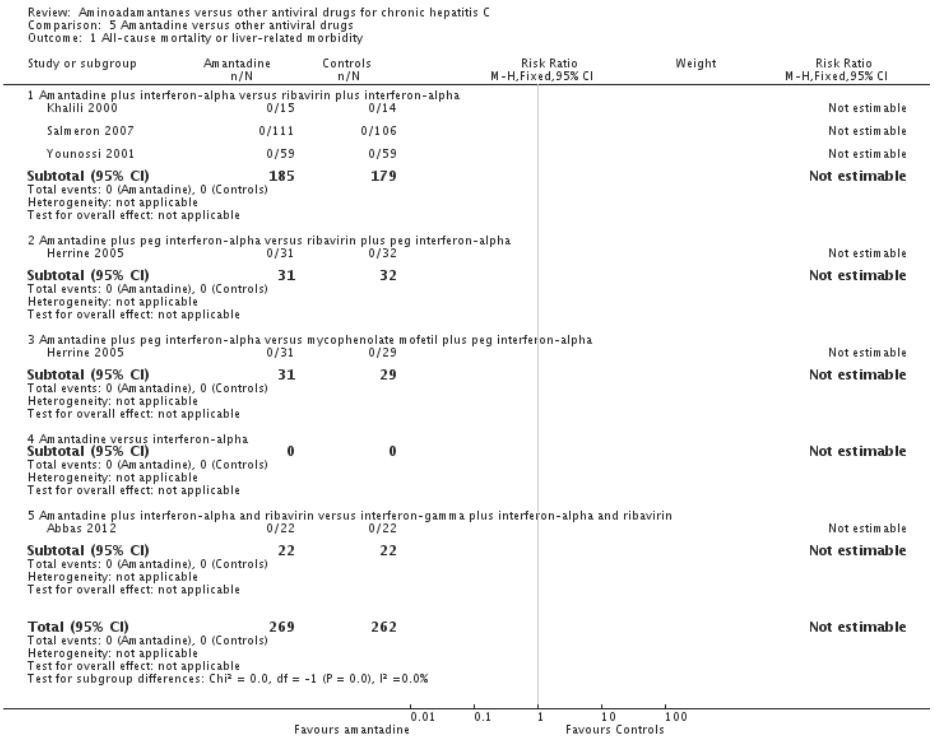
Comparison 5. Amantadine versus other antiviral drugs

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality or liver-related morbidity	5	531	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.1 Amantadine plus interferon-alpha versus ribavirin plus interferon-alpha	3	364	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Amantadine plus peg interferon-alpha versus ribavirin plus peg interferon-alpha	1	63	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Amantadine plus peg interferon-alpha versus mycophenolate mofetil plus peg interferon-alpha	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 Amantadine versus interferon-alpha	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.5 Amantadine plus interferon-alpha and ribavirin versus interferon-gamma plus interferon-alpha and ribavirin	1	44	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Adverse events	6	612	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.37, 1.15]
2.1 Amantadine plus interferon-alpha versus ribavirin plus interferon-alpha	3	364	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.14, 1.03]

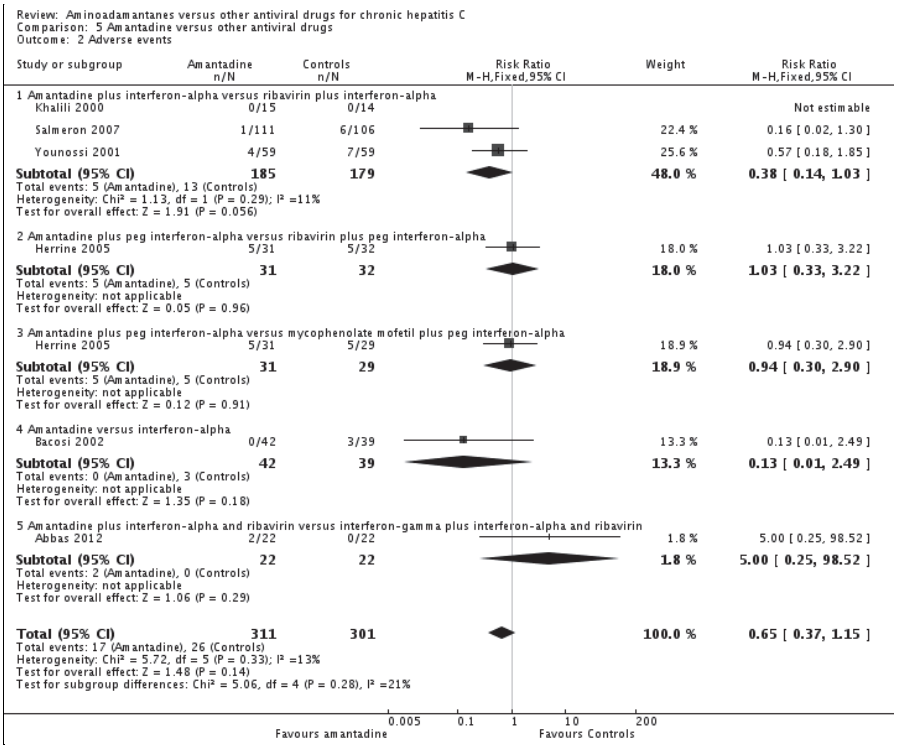
2.2 Amantadine plus peg interferon-alpha versus ribavirin plus peg interferon-alpha	1	63	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.33, 3.22]
2.3 Amantadine plus peg interferon-alpha versus mycophenolate mofetil plus peg interferon-alpha	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.30, 2.90]
2.4 Amantadine versus interferon-alpha	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.13 [0.01, 2.49]
2.5 Amantadine plus interferon-alpha and ribavirin versus interferon-gamma plus interferon-alpha and ribavirin	1	44	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.25, 98.52]
3 Failure of sustained virological response	6	612	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [1.07, 1.22]
3.1 Amantadine plus interferon-alpha versus ribavirin plus interferon-alpha	3	364	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [1.04, 1.18]
3.2 Amantadine plus peg interferon-alpha versus ribavirin plus peg interferon-alpha	1	63	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [1.08, 1.94]
3.3 Amantadine plus peg interferon-alpha versus mycophenolate mofetil plus peg interferon-alpha	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.89, 1.34]
3.4 Amantadine versus interferon-alpha	1	81	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.87, 1.35]
3.5 Amantadine plus interferon-alpha and ribavirin versus interferon-gamma plus interferon-alpha and ribavirin	1	44	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [0.89, 2.37]
4 Failure of end of treatment virological response	5	494	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [1.13, 1.42]
4.1 Amantadine plus interferon-alpha versus ribavirin plus interferon-alpha	2	246	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [1.03, 1.32]
4.2 Amantadine plus peg interferon-alpha versus ribavirin plus peg interferon-alpha	1	63	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.85, 2.39]
4.3 Amantadine plus peg interferon-alpha versus mycophenolate mofetil plus peg interferon-alpha	1	60	Risk Ratio (M-H, Fixed, 95% CI)	2.10 [1.09, 4.08]
4.4 Amantadine versus interferon-alpha	1	81	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.96, 1.62]
4.5 Amantadine plus interferon-alpha and ribavirin versus interferon-gamma plus interferon-alpha and ribavirin	1	44	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [0.82, 2.26]
5 Failure of normalisation of ALT at end of treatment	3	154	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.90, 1.58]
5.1 Amantadine plus interferon-alpha versus ribavirin plus interferon-alpha	1	29	Risk Ratio (M-H, Fixed, 95% CI)	2.02 [1.07, 3.82]
5.2 Amantadine versus interferon-alpha	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.59, 1.33]
5.3 Amantadine plus interferon-alpha and ribavirin versus interferon-gamma plus interferon-alpha and ribavirin	1	44	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [0.82, 2.26]

6 Failure of normalisation of ALT at end of follow-up	4	277	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.99, 1.32]
6.1 Amantadine plus interferon-alpha versus ribavirin plus interferon-alpha	1	29	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.91, 1.48]
6.2 Amantadine plus peg interferon-alpha versus ribavirin plus peg interferon-alpha	1	63	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [1.02, 1.96]
6.3 Amantadine plus peg interferon-alpha versus mycophenolate mofetil plus peg interferon-alpha	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.83, 1.35]
6.4 Amantadine versus interferon-alpha	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.64, 1.25]
6.5 Amantadine plus interferon-alpha and ribavirin versus interferon-gamma plus interferon-alpha and ribavirin	1	44	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [0.89, 2.37]

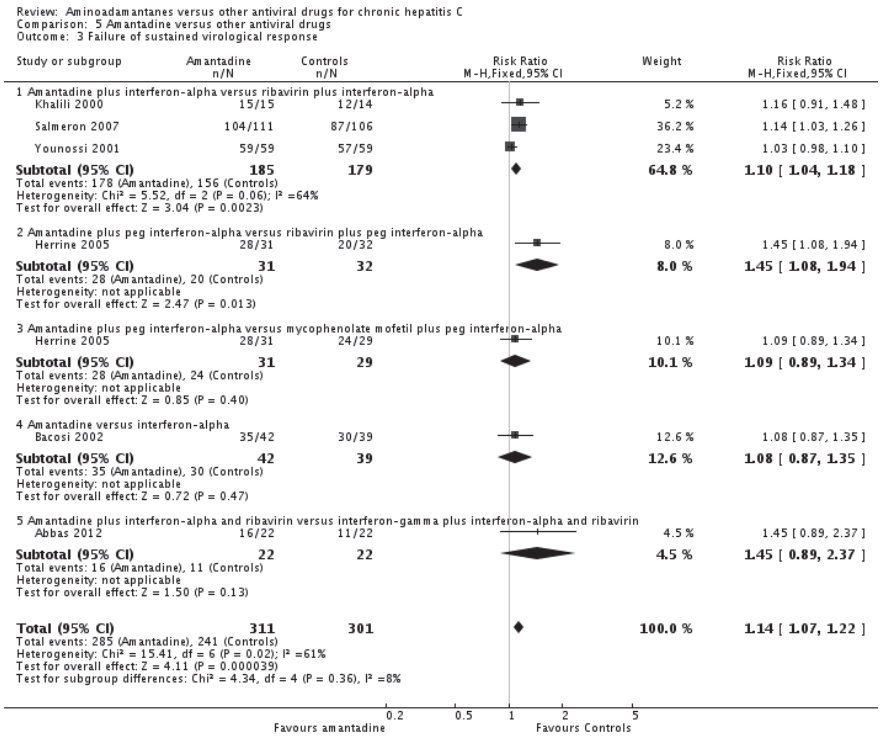
Analysis 5.1. Comparison 5 Amantadine versus other antiviral drugs, Outcome 1 All-cause mortality or liver-related morbidity.



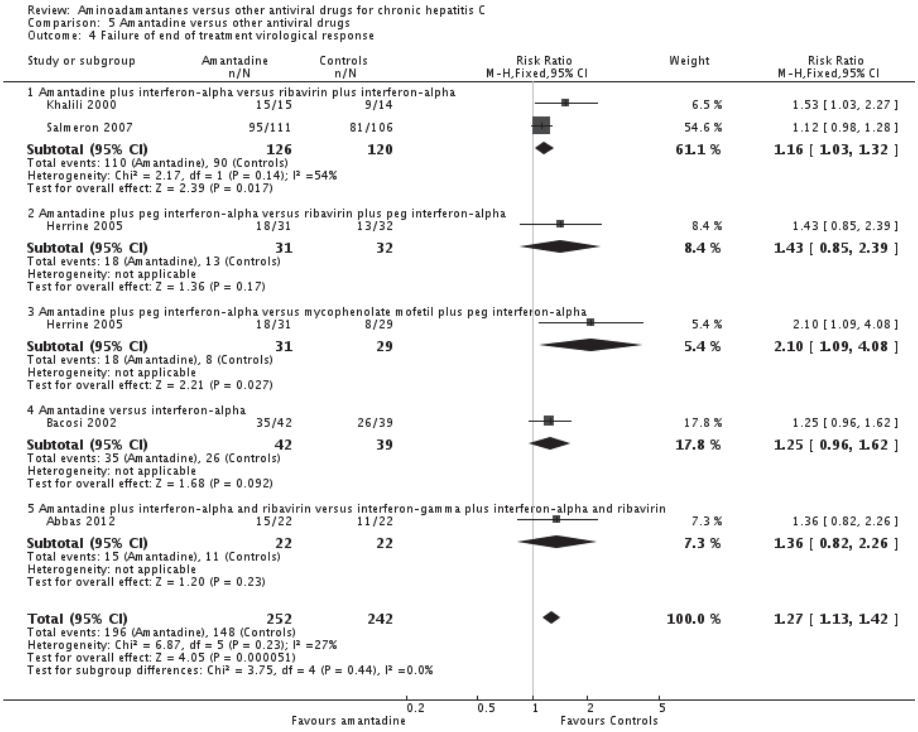
Analysis 5.2. Comparison 5 Amantadine versus other antiviral drugs, Outcome 2 Adverse events.



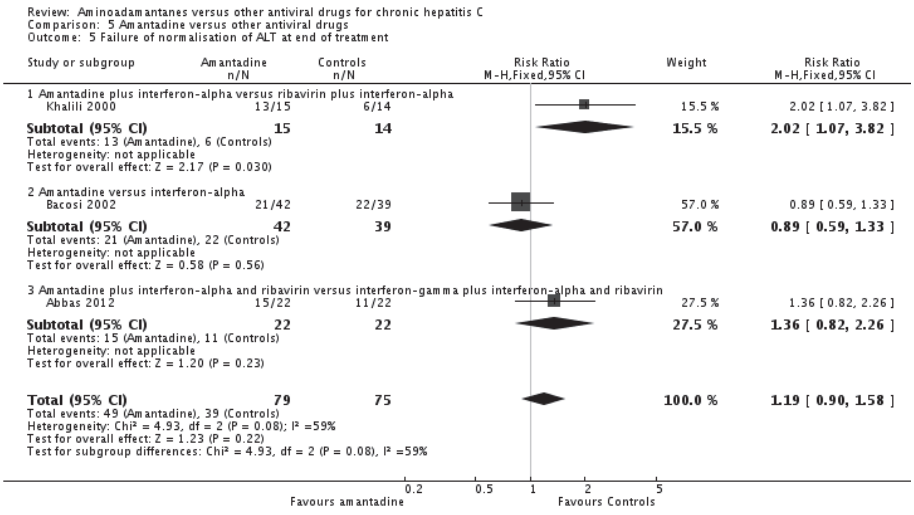
Analysis 5.3 Comparison 5 Amantadine versus other antiviral drugs, Outcome 3 Failure of sustained virological response.



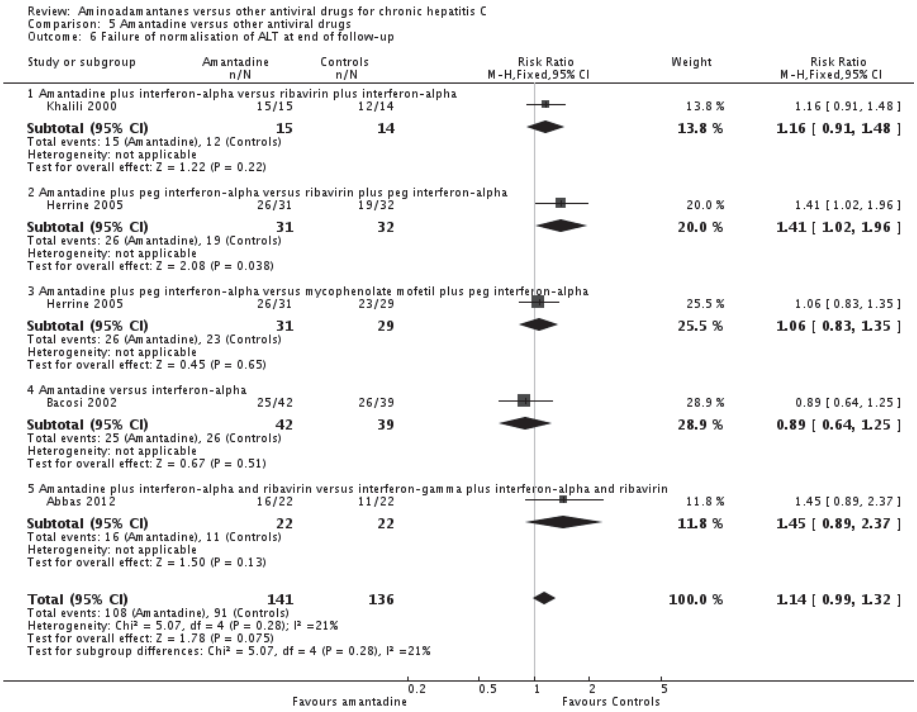
Analysis 5.4. Comparison 5 Amantadine versus other antiviral drugs, Outcome 4 Failure of end of treatment virological response.



Analysis 5.5. Comparison 5 Amantadine versus other antiviral drugs, Outcome 5 Failure of normalisation of ALT at end of treatment.



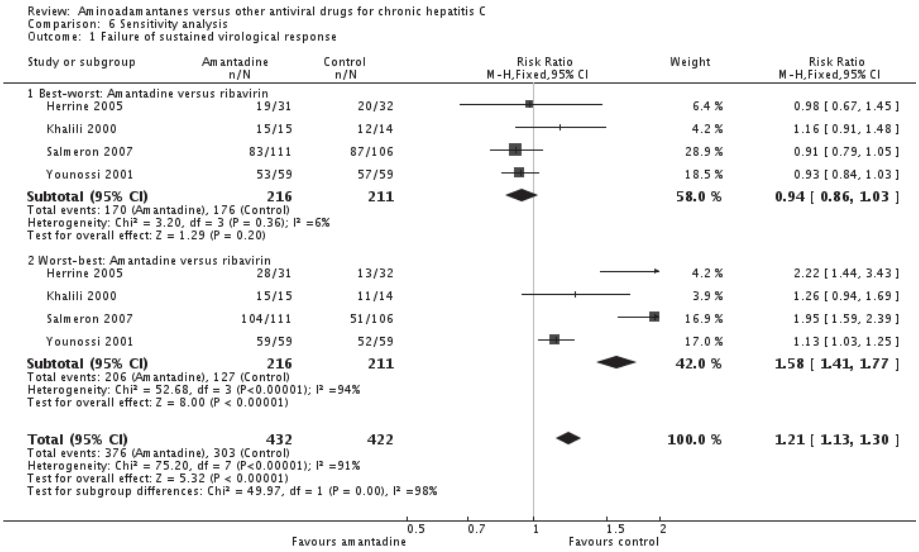
Analysis 5.6. Comparison 5 Amantadine versus other antiviral drugs, Outcome 6 Failure of normalisation of ALT at end of follow-up.



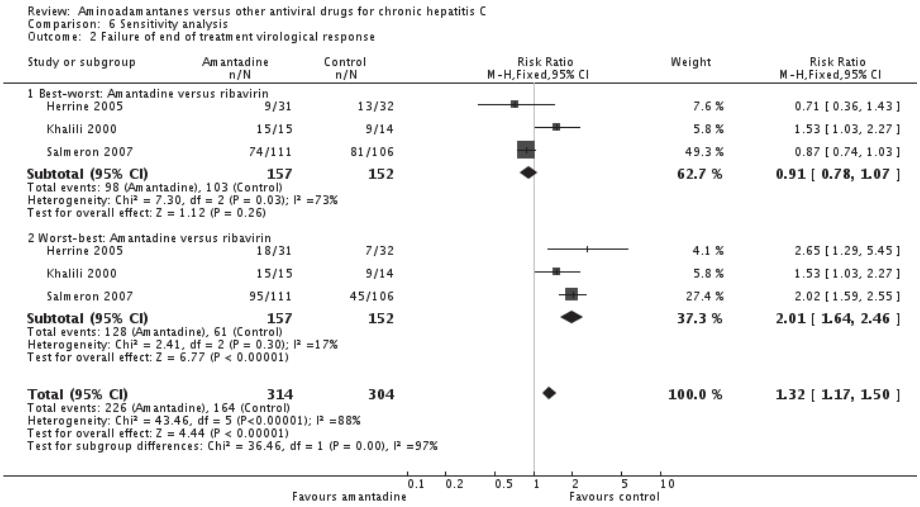
Comparison 6. Sensitivity analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Failure of sustained virological response	4	854	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [1.13, 1.30]
1.1 Best-worst: Amantadine versus ribavirin	4	427	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.86, 1.03]
1.2 Worst-best: Amantadine versus ribavirin	4	427	Risk Ratio (M-H, Fixed, 95% CI)	1.58 [1.41, 1.77]
2 Failure of end of treatment virological response	3	618	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [1.17, 1.50]
2.1 Best-worst: Amantadine versus ribavirin	3	309	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.78, 1.07]
2.2 Worst-best: Amantadine versus ribavirin	3	309	Risk Ratio (M-H, Fixed, 95% CI)	2.01 [1.64, 2.46]

Analysis 6.1. Comparison 6 Sensitivity analysis, Outcome 1 Failure of sustained virological response.



Analysis 6.2. Comparison 6 Sensitivity analysis, Outcome 2 Failure of end of treatment virological response.



Appendices

Appendix 1. Search strategies

Database	Time span	Search strategy
Cochrane Hepato-Biliary Group Controlled Trials Register	1996 to December 2013	(adaman* OR amantadin* OR symmetrel OR symandin* OR rimantadin* OR flumadin* OR methenamin*) AND ('hepatitis C' OR 'hep C' OR HCV)
Cochrane Central Register of Controlled Trials (CENTRAL)	Issue 11 of 12, 2013	#1 MeSH descriptor: [Adamantane] explode all trees #2 adaman* OR amantadin* OR symmetrel OR symandin* OR rimantadin* OR flumadin* OR methenamin* #3 (#1 OR #2) #4 MeSH descriptor: [Hepatitis C] explode all trees #5 hepatitis C OR hep C OR HCV #6 (#4 OR #5) #7 (#3 AND #6)
MEDLINE (Ovid SP)	1946 to December 2013	1. exp Adamantane/ 2. (adaman* or amantadin* or symmetrel or symandin* or rimantadin* or flumadin* or methenamin*).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] 3. 1 or 2 4. exp Hepatitis C/ 5. (hepatitis C or hep C or HCV).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] 6. 4 or 5 7. 3 and 6 8. (random* or blind* or placebo* or meta-analys*).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] 9. 7 and 8
EMBASE (Ovid SP)	1974 to December 2013	1. exp amantadine/ 2. exp rimantadine/ 3. (adaman* or amantadin* or symmetrel or symandin* or rimantadin* or flumadin* or methenamin*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 4. 1 or 2 or 3 5. exp hepatitis C/ 6. (hepatitis C or hep C or HCV).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 7. 5 or 6 8. 4 and 7

		9. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 10. 8 and 9
Science Citation Index Expanded	1900 to December 2013	# 5 #4 AND #3 # 4 TS=(random* or blind* or placebo* or meta-analys*) # 3 #2 AND #1 # 2 TS=(hepatitis C or hep C or HCV) # 1 TS=(adaman* or amantadin* or symmetrel or symandin* or rimantadin* or flumadin* or methenamin*)

Contributions of authors

ML, MB, JD, and CG were involved in the study concept and design.
ML and MB screened the literature, selected publications for inclusion and exclusion according to the eligibility criteria, extracted data, and made the risk of bias judgements.
ML, MB, and CG analysed and interpreted the data and results.
ML drafted the manuscript and performed the meta-analyses.
JD and CG were involved in critical revision of the manuscript for important intellectual content.
All authors approved the review for publication.

Declarations of interest

Mieke H Lamers: no declarations of interest.
Mark Broekman: no declarations of interest.
Joost PH Drenth: no declarations of interest.
Christian Gluud: no declarations of interest.

Sources of support

Internal sources

- Radboud University Medical Center Nijmegen, Netherlands.

External sources

- The Cochrane Hepato-Biliary Group (CHBG), Denmark.

The first author, Mieke H Lamers, worked on the review for three months at the CHBG Editorial Team offices.

Differences between protocol and review

We conducted sensitivity analysis on only the statistical significant findings with only 'best-worse' case scenario and 'worst-best' case scenario (instead of these two with poor outcome analysis and good outcome analysis in both intervention groups) in order to check the robustness of our analysis.

Characteristics of studies

Characteristics of included studies [ordered by study ID]

Abbas 2012

Methods	Randomised trial in genotype 3 patients, non-responders or relapsers. 48 weeks therapy, 24 weeks follow-up.
Participants	**Country:** Pakistan. **Inclusion criteria:** adult male and female patients infected with HCV genotype 3, ranging in age from 18-70 years, who had previously received standard interferon alpha 2a or 2b 3 MU thrice a week in combination with ribavirin (800 mg to 1200 mg) for 24 weeks and had not shown a response as depicted by disappearance of HCV RNA from serum dose in the last month of therapy (non-responders) or who relapsed at six months post-treatment (relapsers). Hb ≥ 10 g/dL (females) and ≥ 11 g/dL (males), platelet count ≥ 100 x 10^9/L, at least one abnormal ALT value in the last year, normal TSH, non-pregnant adult females and absence of drug or alcohol abuse. **Exclusion criteria:** antiviral therapy in the last three months, hepatitis B or HIV co-infection, severe renal dysfunction or creatinine clearance less than 50 mL/min, pregnant or breast feeding women, suspected hypersensitivity to Interferon alpha, gamma or ribavirin, decompensated liver cirrhosis, history or any evidence of other concomitant causes of chronic liver disease, active malignant disease, any known pre-existing medical condition that could interfere with the patient's participation or completion of study. **Amantadine group:** 22 patients, mean age 42.32 ± 8.5 years, male/female = 13/9. Basal viral load was 947214.6 ± 1266694.8 IU/mL, ALT was 103.05 ± 55.6 IU/L Genotype 3: 22. Patient with F3 or F4 fibrosis: 7. **Control group:** 22 patients, mean age 44.95 ± 10.1 years, male/female = 15/7. Basal viral load was 606691.2 ± 872128.9 IU/mL, ALT was 88.82 ± 65.4 IU/L Genotype 3: 22. Patient with F3 or F4 fibrosis: 7.

Interventions	**Amantadine group:** amantadine 100 mg twice a day, interferon-alpha 2b 3 MU thrice a week, and ribavirin 800 mg to 1200 mg per day. Patients of less than 70 kg of weight received 800 mg of ribavirin, while 70 kg or above received 1200 mg daily. **Control group:** interferon-gamma 200 MU thrice a week in place of amantadine.
Outcomes	Mortality; Liver-related morbidity; SAE; Treatment discontinuation due to AE; Number of patients without SVR; Number of patients with detectable HCV RNA at EOT; Number of patients without normalisation of ALT at EOT and at EOFU.
Notes	General note for amantadine: ML sent an email to Novartis (a pharmaceutical company which produces amantadine) mid.phnlar@novartis.com on 18 December 2013. They answered that no new research with amantadine has been done.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Randomisation, enrolment of participants and assignments of participants to interventions was done by the principle investigator, insufficient information.
Allocation concealment (selection bias)	Low risk	Opaque sealed envelope method.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded, these interventions were not be delivered in identical ways.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded, these interventions were not be delivered in identical ways.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data.
Selective reporting (reporting bias)	High risk	Only virological response at 72 weeks, biochemical response at 72 weeks, and safety and tolerance were mentioned in the patients and methods session (however, more data were given in the results section). Not every outcome we would suggest was reported on.
Other bias	Low risk	For-profit bias: the study includes the off-label use of the drug. The cost of the drugs and the PCR-based investigations were funded by the Genetech Biopharm Pakistan. No limitations on publication were imposed by the sponsor. No baseline imbalance; sample size calculation was not reported, the trials was not stopped early.

Bacosi 2002

Methods	Randomised trial in non-responders or relapsers. 12 months therapy, 12 months follow-up.
Participants	**Country:** Italy. 165 patients were screened (females n = 86; males n = 79) for 3 groups (55 patients each group). **Inclusion criteria:** detectable, circulating HCV RNA; presence of chronic active liver disease already diagnosed on the grounds of laboratory and pathologic findings.

	Exclusion criteria: Child-Pugh score B or C, previous episode of gastrointestinal bleeding, disturbances of cardiac rhythm as determined by electrocardiogram and renal failure. **Amantadine group:** 42 patients, mean age 68 ± 3 years, male/female = 18/24. Serum ALT was not provided and the basal viral load 482 ± 227 x 10^3 copies per mL. Genotype 1b was predominant (n = 39) with three patients with mixed genotypes. The other three patients had genotypes 2a (n = 1), 2a-2b (n = 1) and 2a to 2c (n = 1). 2 patients cirrhosis. **Control group:** 39 patients, mean age 65 ± 2 years, male/female = 18/21. Basal viral load was 637 ± 452 x 10^3 copies per mL, ALT was not provided. Genotype 1b was predominant (n = 31) associated with 1a in three cases; the remaining 8 patients had genotypes (2a (n = 4), 2a to 2c (n = 3) and 4 (n = 1). No patient with cirrhosis.
Interventions	**Amantadine group:** 100 mg amantadine oral twice daily. **Control group:** interferon-alpha-n_3 6 MU sc every other day until return to normal of ALT or a decrease in viral copies of at least 1 log unit (however, no longer than 3 months) then followed by 3 MU. **Another included group** received interferon-alpha-n_3 6 MU sc every other day until return to normal of ALT or a decrease in viral copies of at least 1 log unit (however, no longer than 3 months) then followed by 3 MU plus 200 mg/day amantadine orally. The duration of the trial treatment was 12 months; treatment, however, did not exceed 9 months in those patients who received amantadine and who did not show a decrease of at least 1 log unit in viral copies. Furthermore, treatment did not exceed 6 months in those patients who received interferon-alpha-n_3 if there was no significant decrease in viral load.
Outcomes	SAE; Treatment discontinuation due to AE; Number of patients without SVR; Number of patients with detectable HCV RNA at EOT; Number of patients without normalisation of ALT at EOT and at EOFU.
Notes	ML send Dr Bacosi an email for additional information at 13/12/2011.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information.
Allocation concealment (selection bias)	High risk	Closed envelopes, although not opaque.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded, these interventions were not be delivered in identical ways.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded, these interventions were not be delivered in identical ways.
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropouts not equally divided. Many patients dropped out after randomisation.
Selective reporting (reporting bias)	High risk	No clear primary and secondary outcome measures mentioned.
Other bias	Unclear risk	For-profit bias: insufficient information.

		No baseline imbalance; sample size calculation was not reported, the trial was not stopped early.

Herrine 2005

Methods	Randomised, controlled, multicentre trial in relapsers or patients who had a viral breakthrough. 48 weeks therapy, 24 weeks follow-up.
Participants	**Country:** United States of America. 124 patients were randomised, 123 received at least one dose of study medication. **Inclusion criteria:** adult patients with serologic evidence of HCV infection, by a positive anti-HCV antibody test and detectable HCV RNA in serum, who had a virologic response during treatment with standard interferon-alpha-2b plus ribavirin and had relapsed after at least 24 weeks of treatment or had a virologic breakthrough while still on treatment; serum ALT activity above the upper limit of normal during the 6 months before entering the study; liver biopsy consistent with chronic HCV infection in the previous 36 months; and a minimum of 24 weeks since cessation of standard interferon-alpha-2b plus ribavirin treatment, with no interferon therapy during this time. **Exclusion criteria:** had received any systemic antiviral therapy within 24 weeks of the start of the study or were expected to need any systemic antiviral therapy during the study or had acute hepatitis A or B infection, HIV infection, decompensated liver disease, neutropenia (<1500 neutrophils/mm^3), anaemia (Hb < 12 g/dL in women and < 13 g/dL in men), thrombocytopenia (platelets, < 90,000/mm^3), serum creatinine level higher than 1.5 times the upper limit of normal, history of alcohol or drug abuse within 1 year of entry, history of severe psychiatric disease, serum α-fetoprotein level >100 ng/mL, or substantial coexisting medical conditions. **Amantadine group:** 31 patients, mean age 46 years, male/female = 19/12, BMI not provided. Mean serum ALT 57 SE 7 IU/L, mean AST 47 SE 8 IU/L, basal viral load ≤ 800.000 IU/mL: 14, and > 800.000 IU/mL: 17. Genotype 1 (n = 26) and genotype non-1 (n = 5). Histological staging: non-cirrhosis = 27; cirrhosis = 4. **Control group 1 with ribavirin:** 32 patients, mean age 48 years, male/female = 24/8, BMI not provided. Mean serum ALT 75 SE 10 IU/L, mean AST 60 SE 7 IU/L, basal viral load ≤ 800.000 IU/mL: 14, and > 800.000 IU/mL: 18. Genotype 1 (n = 25) and genotype non-1 (n = 7). Histological staging: non-cirrhosis = 23; cirrhosis = 9. **Control group 2 with mycophenolate mofetil:** 29 patients, mean age 48 years, male/female = 20/9, BMI not provided. Mean serum ALT 69 SE 9 IU/L, mean AST 47 SE 6 IU/L, basal viral load ≤ 800.000 IU/mL: 10, and > 800.000IU/mL: 19. Genotype 1 (n = 23) and genotype non-1 (n = 6). Histological staging: non-cirrhosis = 28; cirrhosis = 1.
Interventions	Patients were randomly assigned at a 1:1:1:1 ratio to: **Amantadine group:** sc weekly injections of 180 µg peg interferon-alpha-2a plus orally administered amantadine 200 mg/day. **Control group 1 with ribavirin:** peg interferon-alpha-2a plus orally administered ribavirin, 800 mg/day in split doses for patients weighing < 75 kg and 1000 mg/day in split doses for those weighing ≥ 75 kg, both for 48 weeks.

	Control group 2 with mycophenolate mofetil: peg interferon-alpha-2a plus mycophenolate mofetil for 48 weeks with a daily dose of mycophenolate mofetil of 1 g twice daily. Another included group received peg interferon-alpha-2a and orally administered ribavirin plus amantadine in the same dosages as mentioned above. Randomiation was stratified according to HCV genotype (type 1 vs. non-type 1, with any patient positive for both type 1 and non-type 1 categorised as type 1), viral load (≤ 800,000 or > 800,000 IU/mL), and relapse vs. breakthrough.
Outcomes	Mortality; Liver-related morbidity; SAE; Treatment discontinuation due to AE; Number of patients without SVR; Number of patients with detectable HCV RNA at EOT; Number of patients without normalisation of ALT at EOFU.
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information.
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded, these interventions were not be delivered in identical ways.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded, these interventions were not be delivered in identical ways.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information. Withdrawals mentioned, but not the reason for withdrawal in all patients.
Selective reporting (reporting bias)	High risk	Only virological response at 72 weeks, biochemical response at 72 weeks, and safety were mentioned in the patients and methods session (however, more data were given in the results section). Not every outcome we would suggest was reported on.
Other bias	High risk	For-profit bias: high: research grant Roche. No baseline imbalance; sample size calculation was reported, the trial was not stopped early.

Khalili 2000

Methods	Randomised, clinical trial in patients who had previously failed to respond to interferon-alpha monotherapy. 24 weeks therapy, 24 weeks follow-up.
Participants	**Country:** United States of America. A total of 31 consecutive patients were enrolled. Two of the 31 patients were noncompliant and were disenrolled after 1 and 8 wk of treatment. **Inclusion criteria:** Abnormal ALT during the last month of interferon treatment and persistent elevation for ≥ 6 months before entry; presence of HCV RNA at baseline by quantitative branched nucleotide assay (Chiron bDNA 2.0; Chiron, Emeryville, CA); and a liver biopsy within 18 months before entry

	consistent with chronic hepatitis C. All participants had clinically compensated liver disease as determined by prothrombin time < 2 sec prolonged, serum albumin > 3.5 g/dL, direct bilirubin < 0.3 mg/dL, indirect bilirubin < 0.8 mg/dL, absence of ascites, hepatic encephalopathy, or a past history of variceal bleeding. Baseline complete blood counts before entry required a Hb level > 12 g/dL, white cell count > 3,000/mm^3, and platelets > 100,000/mm^3. **Exclusion criteria:** therapy with antiviral agents or immunosuppressive therapy within 6 months before entry, evidence for another possible etiology for the liver disease, coinfection with HBV or HIV, pregnancy or inability to practice birth control, other significant medical illness, an abnormal a-fetoprotein level, and active alcohol (> 80 g/day) or substance abuse. **Amantadine group:** 15 patients, mean age 49.2 years, male/female = 9/6, BMI not provided. Mean serum ALT 145 IU/L, mean basal viral load 3.48 x 10^6 copies/mL. Genotype 1 = 13, genotype 3 = 1 and indeterminate genotype = 1. Fibrosis on liver biopsy = 9. **Control group:** 14 patients, mean age 41.3 years, male/female = 12/2, BMI not provided. Mean serum ALT 130 IU/L, mean basal viral load 2.22 x 10^6 copies/mL. Genotype 1 = 11, genotype 2 = 1, and genotype 3 = 2. Fibrosis on liver biopsy = 5.
Interventions	**Amantadine group:** a 24-wk course of interferon-alpha-2b given subcutaneously three times weekly in combination with amantadine hydrochloride, 200 mg daily given in two divided doses. **Control group:** an identical course of interferon-alpha combined with ribavirin, 1000 mg daily.
Outcomes	Mortality and liver-related morbidity; SAE; Treatment discontinuation due to AE; Number of patients without SVR; Number of patients with detectable HCV RNA at EOT; Number of patients without normalisation of ALT at EOT and at EOFU.
Notes	The sensitivity limit of the PCR assay was 100 copies/mL.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information.
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded, these interventions were not be delivered in identical ways.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded, these interventions were not be delivered in identical ways.
Incomplete outcome data (attrition bias) All outcomes	Low risk	In the control group only 1 patient was lost to follow-up.
Selective reporting (reporting bias)	High risk	No clear primary and secondary endpoints were mentioned in the 'materials and methods' section. Not every outcome we would suggest was reported on.

Other bias	Unclear risk	For-profit bias: insufficient information. There was baseline imbalance regarding age in both groups; sample size calculation was not reported, the trial was not stopped early.

Salmeron 2007

Methods	Randomised, parallel-group trial in interferon non-responder patients in 36 centres. Patients were recruited between 1999 and 2001 and the follow-up finished in March 2003. 48 weeks therapy, 24 weeks follow-up.
Participants	**Country:** Spain. 378 patients were randomised. **Inclusion criteria:** serum HCV RNA positivity by PCR before the beginning of the treatment and serum ALT activity above the upper limit of normal with at least one value during the 6-month period preceding the initiation of test drug dosing. All patients had chronic hepatitis without cirrhosis in the biopsy. The biopsies had been carried out up to a maximum of 3 years before entering the study. A treatment-free interval of at least 6 months was necessary between the first and the second course. **Exclusion criteria:** age 60 years or older, evidence of any cause of liver disease other than chronic HCV (coinfection with hepatitis B virus or HIV, concomitant autoimmune disease or metabolic disease). Clinically significant cardiovascular, renal, haematological, rheumatological, neurological or psychiatric disease, systemic infections, neoplastic disease, organ grafts and systemic immunosuppressive treatment. Active alcohol (alcohol intake > 40 g/day in females and > 60 g/day in males) or drug abuse within the previous year. Pregnancy or lactation period. Hb levels < 12 g/dL, white cell count < 3000/mm^3, granulocyte count < 1500/mm^3 or platelet count <100 000/mm^3. **Amantadine group + interferon-alpha:** 111 patients, mean age 44.7 ± 9 years, male/female = 87/24. Mean weight 78 ± 13 kg. Mean serum ALT 133 ± 90 UI/L, mean serum AST 94 ± 81 UI/L, and high serum HCV RNA titre > 8 x 10^5 UI/mL was detected in 34 of 78 patients. Genotype 1: 72 of 88, genotype non-1: 16 of 88. Histological staging was not provided. **Control group ribavirin + interferon-alpha:** 106 patients, mean age 46 ± 9 years, male/female = 85/21. Mean weight 77 ± 13 kg. Mean serum ALT 124 ± 92 UI/L, mean serum AST 79 ± 75 UI/L, and high serum HCV RNA titre > 8 x 10^5 UI/mL was detected in 29 of 81 patients. Genotype 1: 74 of 85, genotype non-1: 11 of 85. Histological staging was not provided.
Interventions	**Amantadine group + interferon-alpha:** interferon a-2a, 9 MU/day sc for 4 weeks and 3 MU 3 times a week for a further 44 weeks plus amantadine chloride, 100 mg twice per day. **Control group ribavirin + interferon-alpha:** the same doses of interferon-a-2a plus ribavirin 1000 mg to 1200 mg daily in two gifts. Two other included groups received: Group 1. Interferona-2a, 9 MU/day sc for 4 weeks and 3 MU 3 times a week for a further 44 weeks. Group 2. The same doses of interferona-2a plus amantadine 100 mg twice per day, and ribavirin, 1000 mg to 1200 mg per day according to weight.

Outcomes	Mortality; Liver-related morbidity; SAE; Treatment discontinuation due to AE; Number of patients without SVR; Number of patients with detectable HCV RNA at EOT.	
Notes	ML has send an email to Dr. Salmeron about the ALT values at EOT and at 6 months FU at 10-01-2012.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Patients were selected randomly by central telephone.
Allocation concealment (selection bias)	Low risk	Patients were selected randomly by central telephone.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded, these interventions were not be delivered in identical ways.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded, these interventions were not be delivered in identical ways.
Incomplete outcome data (attrition bias) All outcomes	High risk	All dropouts were discussed, but not equally divided over groups.
Selective reporting (reporting bias)	High risk	Not all of the study's pre-specified primary outcomes have been reported. The biochemical response (normalisation of serum ALT) was not reported, although it was mentioned as study end point in the article.
Other bias	High risk	For-profit bias: Roche. No baseline imbalance; sample size calculation was reported, the trial was stopped early due to the poor results

Younossi 2001

Methods	Randomised, double-blind, clinical, multicentre trial. 24 weeks therapy, 24 weeks follow-up.
Participants	**Country:** United States of America. **Inclusion criteria:** adult patients with chronic hepatitis C who had previously received at least one course of recombinant interferon alpha (interferon alpha-2b; interferon alpha-2a and interferon n3) at a dose of 3.3 ± 2.0 MU three times per week for at least 12 weeks and who showed neither biochemical nor virologic response (elevated ALT and HCV RNA positive by PCR) were considered for the study. All potential candidates fully consented and those who agreed to participate and met all the inclusion and exclusion criteria were offered to enrol in the study. **Exclusion criteria:** decompensated liver disease, immunocompromised or HIV positivity, severe psychiatric conditions, poorly controlled diabetes mellitus, active cardiopulmonary disease, renal insufficiency, seizure disorders, autoimmune disease, uncontrolled thyroid disease and other liver diseases. Those with Hb <13 g/dL for males and < 12 g/dL for females, platelets count <100 000/mm^3 and WBCs < 3000/mm^3. **Amantadine group + interferon-alpha:** 59 patients, mean age 45.6 ± 7.7 years, male/female = 36/23. Mean BMI 29.1 ± 6.9 kg/m^2. Mean serum ALT 121 ± 77.9

	IU/L, and serum HCV RNA titre > 2 x 10^6 UI/mL was detected in 43 of 59 patients. Genotype 1: 43 of 59, genotype non-1: 15 of 59. Histological staging: non-cirrhosis = 49; cirrhosis = 10. Some patient-data are missing. **Control group ribavirin + interferon-alpha:** 59 patients, mean age 46.1 ± 6.8 years, male/female = 37/22. Mean BMI 28.4 ± 5.1 kg/m^2. Mean serum ALT 139 ± 11 IU/L, and serum HCV RNA titre > 2 x 10^6 UI/mL was detected in 40 of 59 patients. Genotype 1: 49 of 59, genotype non-1: 10 of 59. Histological staging: non-cirrhosis = 48; cirrhosis = 10. Some patient-data are missing.. Health-related quality of life (HRQL) was assessed at baseline and every 3 months using the medical outcome study Short Form-36 (SF-36) and a validated liver disease-specific instrument, Chronic Liver Disease Questionnaire (CLDQ).	
Interventions	**Amantadine group:** interferon alpha-2b at a dose of 3 MU three times weekly and amantadine 200 mg daily in two divided doses. **Control group:** interferon alpha-2b at a dose of 3 MU three times per week and ribavirin 800 mg daily in two divided doses.	
Outcomes	SAE; Treatment discontinuation due to AE; QoL.	
Notes	ML send dr. Younossi an email at 8-1-2013 about the exact numbers of patients who achieved virological and biochemical response.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The randomisation process was centrally administered by the data manager through telephone contact. Random, permuted blocks were used to ensure balance between the number of patients assigned to each treatment arm and to make it difficult for study personnel to know where blocks started and stopped.
Allocation concealment (selection bias)	Low risk	The randomisation process was centrally administered by the data manager through telephone contact.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	In order to keep the study blinded, patients receiving one treatment regimen also received the identical placebos of the alternative regimen. Regardless of the treatment arm, each patient received identical and equal numbers of pills.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information. Withdrawals mentioned, but not the reason for withdrawal in all patients. What happened to 6 interferon alpha + amantadine and 5 interferon alpha + ribavirin patients?
Selective reporting (reporting bias)	High risk	Numbers in table are not corresponding with numbers in text for example, patients achieving SVR and biochemical response. No histological outcomes.
Other bias	High risk	For-profit bias: Unrestricted grant from Integrated Therapeutics, Schering-Plough Oncology Biotech. No baseline imbalance; sample size calculation was not reported, the trial was not stopped early.

AE: adverse event
ALT: alanine aminotransferase
AST: aspartate transaminase

BMI: body mass index
EOFU: end of follow-up
EOT: end of treatment
Hb: haemoglobin
HBV: hepatitis B virus
HCV: hepatitis C virus
HIV: human immunodeficiency virus
IU/L: international units per litre
MU: million units
PCR: polymerase chain reaction
QoL: quality of life
RNA: ribonucleic acid
SAE: serious adverse event
sc: subcutaneous
SE: standard error
SVR: sustained virological response
TSH: thyroid-stimulating hormone
U/L: units per litre
vs: versus
WBC: white blood cells
wk: week

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Bellobuono 2002	After three months, all viraemic patients were treated with triple combination therapy (addition of amantadine or ribavirin). Groups were equally treated after three months and so a separate comparison between amantadine and ribavirin is not possible.
Di Bisceglie 2001	Only preliminary findings, no outcome measures we can include.
Gerardi 1998	Unclear study design, no outcome measure, groups not comparable.
Torre 1999	Outcome measure only after 30 days of therapy, not after 6 or 12 months of therapy.

Characteristics of studies awaiting assessment [ordered by study ID]

Ideo 2003

Methods	Randomised, multicentre trial in 49 centres.
Participants	**Country**: Italy 784 biopsy-proven chronic hepatitis C, HCV RNA positive, and persistently elevated ALT, naive patients.
Interventions	Pegylated interferon-alpha-2a with ribavirin 1 to 1.2 g daily or amantadine 200 mg daily for 48 weeks with a 24-week follow-up.
Outcomes	SVR

Montaser 2003

Methods	Randomised trial.
Participants	**Country**: Egypt Eighty patients with hepatitis C were selected and divided randomly into four equal groups.
Interventions	All groups were treated for 12 months. Group 1: dimethyl dimethoxy biphenyl dicarboxylate (DDB); Group 2: amantadine; Group 3: DDB and amantadine.Group 4: Sylimarine (control group). 6 months follow-up.
Outcomes	HCV RNA, bilirubin, AST, and alpha fetoprotein levels at unknown time points.

Picciotto 1999

Methods	Randomised trial.
Participants	**Country**: USA Twenty patients with a diagnosis of chronic hepatitis C, based on the consistent detection of anti-HCV antibody, raised level of ALT, histological examination, never treated before. All patients were hepatitis B surface antigen negative and negative for the antibody of HIV.
Interventions	Interferon-alpha 3 MU daily or interferon-alpha 3 MU daily plus amantadine 200 mg or interferon-alpha 3 MU daily plus ribavirin 1 to 1.2g for 6 months.
Outcomes	HCV RNA and ALT at end of therapy.

Pimstone 1997

Methods	Randomised trial between July and November 1996.
Participants	**Country**: USA Chronic hepatitis C patients who previously failed interferon-alpha therapy. **Amantadine group**: 11 patients **Rimantadine group**: 9 patients
Interventions	Amantadine or rimantadine, 100 mg oral twice daily for 6 months.
Outcomes	ALT and HCV RNA, both prior to treatment and every three months on treatment.

ALT: alanine aminotransferase
AST: aspartate aminotransferase
HCV: hepatitis C virus
HCV RNA: hepatitis C virus ribonucleic acid
HIV: human immunodeficiency virus
MU: million units
SVR: sustained virological response
USA: United States of America

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6

Treatment of hepatitis C monoinfection in adults – Dutch national guidelines

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Abstract

In this new Dutch guideline for hepatitis C virus infection we provide recommendations for the management of hepatitis C infection. Until now the standard for treatment consisted of pegylated interferon alpha (peg-IFNα) and ribavirin. The advent of 1st generation direct antiviral agents such as boceprevir and telaprevir has changed the concept of treatment of adult chronic hepatitis C genotype 1 infected patients.

There are three benefits of boceprevir and telaprevir. They increase the likelihood of cure in (1) naive genotype 1 patients and (2) in patients who did not respond to earlier treatment with peg-IFNα and ribavirin, while allowing (3) shortening of treatment duration from 48 weeks to 24 or 28 weeks which is possible in 40-60% of non-cirrhotic naive (boceprevir and telaprevir) and relapsing patients (telaprevir).

The use of boceprevir and telaprevir is associated with multiple side effects and awareness of these side effects is needed to guide the patient through the treatment process.

This guideline, formulated on behalf of The Netherlands Association of Hepato-gastroenterologists, The Netherlands Association of Internal Medicine and The Dutch Association for the Study of Liver Disease, serves as a manual for physicians for the management and treatment of acute and chronic hepatitis C virus monoinfection in adults.

Introduction

Hepatitis C virus (HCV) infection resulting in chronic liver disease is highly prevalent in Europe.(1) With the introduction of interferon therapy, later combined with ribavirin, eradication of HCV infection became reality. The last innovation in this field came a decade ago with the introduction of pegylated interferon α (peg-IFNα). Further advances in the therapy of HCV infection were in most part restricted to refinements of the existing dual therapy with peg-IFNα and ribavirin (combination abbreviated to PR).

The watershed in the field came with the clinical introduction of two direct-acting antiviral agents (DAAs) boceprevir (Victrelis®) and telaprevir (Incivo®). From 2012 these two DAAs have been allowed on the market in The Netherlands and are reimbursed by the health insurance companies for the treatment of chronic HCV genotype 1 infection in adults with compensated liver disease (including cirrhosis). Phase 3 studies, including more than 2700 patients, have documented the high antiviral potency of these agents against HCV genotype 1.(2-6) Accordingly, the treatment of chronic HCV genotype 1 infected patients has changed and led to the introduction of new national guidelines in several countries, and an update of the EASL and AASLD guidelines.(7-9) The last Dutch guideline on treatment of HCV infection stems from 2008.(10) In order to guide the clinician through the changed therapeutic environment we provide the reader with a completely revised guideline with concise recommendations for the management and treatment of HCV monoinfection in adults. For the complete guideline we refer to www.mdl.nl.

Background

The clinical progression of chronic HCV infection varies among patients. Some have only minimal structural hepatic changes even after prolonged infection, while others rapidly develop complications such as cirrhosis and hepatocellular carcinoma (HCC).(11, 12) The progression of histological deterioration is independent of HCV genotype and the concentration of HCV RNA in plasma (viral load), but is related to host factors such as gender, obesity, presence of concomitant liver disease, life style aspects (e.g. alcohol use), and the existence of an untreated co-infection with hepatitis B virus (HBV) or human immunodeficiency virus (HIV).(13-15)

The overall mortality is increased due to cirrhosis and HCC, but also due to an increased risk of extrahepatic manifestations such as cardiovascular and renal diseases.(16, 17) In contrast,

curing HCV infection with antiviral therapy diminishes the risk of cirrhosis and HCC and consequently improves survival compared to patients with persistent viremia.(18, 19)

There are at least 6 distinct HCV genotypes. In The Netherlands, ~50% of chronic hepatitis C is caused by genotype 1a and 1b, ~30% by genotype 3, whereas genotype 2 and 4 both account for ~10% of chronic HCV infected patients. Genotype 5 and 6 are uncommon in The Netherlands.(20, 21)

Table 1. Treatment responses

Category	Characteristics
Rapid Viral Response (RVR)	HCV RNA undetectable at week 4
Extended Rapid Viral Response (eRVR)	HCV RNA undetectable at week 4 and week 12
Early Viral Response (EVR)	HCV RNA undetectable at week 12 or a decrease by > 2 log
Delayed Viral Response (DVR)	> 2 log decrease but detectable at week 12, undetectable at week 24
End of Treatment Response (ETR)	HCV RNA undetectable at end of treatment
Sustained Viral Response (SVR)	HCV RNA undetectable after 24 weeks of follow-up

The primary goal of therapy is to eliminate HCV infection which is defined as undetectable plasma HCV RNA 24 weeks after termination of treatment defined as sustained virological response (SVR) (see Table 1 for abbreviations). With PR given for 24 or 48 weeks, SVR can be achieved in 40-60% in HCV genotype 1 or 4 infected patients and in 70-80% of patients infected with HCV genotype 2 or 3.(9, 22, 23)

Natural history

In Europe, the incidence of acute HCV infection is around 1 per 100.000 persons per year. This probably underestimates the true incidence because acute HCV infection is asymptomatic in approximately 80% of cases.(9) After infection, formation of HCV antibodies can take months, which implies that plasma HCV RNA analysis should be used to diagnose acute HCV infection.(24)

Spontaneous clearance of HCV infection occurs in 20-30%. Spontaneous clearance is unlikely to happen 12 weeks after infection and treatment should subsequently be initiated to prevent development of chronic HCV infection.(25, 26)

Persistence of plasma HCV RNA for more than 6 months constitutes a chronic HCV infection. It is thought that chronic hepatitis C affects ~ 3% of the world population, i.e. 170 million individuals.(27) The prevalence in The Netherlands varies between 0.1-0.4%.(28, 29) European prevalence rates are higher (0.4-4%).(30) Chronic hepatitis C progresses slowly, over a time frame of 15-50 years. Cohort studies suggest that 10-20% of all infected patients will eventually develop end-stage liver disease, typically after two to three decades.(12, 31) In cirrhotic patients, the annual rate of HCC is 1-4% and chronic hepatitis C induced HCC accounts for one-third of all HCCs.(11)

Initial evaluation

As of 2012 treatment of hepatitis C in The Netherlands is preferably restricted to one of the 40 certified and specialized viral hepatitis treatment centers.(32)

The initial evaluation of a chronic hepatitis C patient consists of a detailed medical history evaluation, which includes assessment of the source of the HCV infection, presence of current or past alcohol abuse, and use of concomitant medication. Evaluation includes physical examination with special attention to signs of chronic liver disease, cirrhosis and liver failure (e.g. spider nevi, palmar erythema, gynecomastia, ascites). Laboratory tests should include full blood count, liver enzymes and function, thyroid and kidney function, and plasma HCV RNA and genotype.(10) Current guidelines recommend vaccination against hepatitis A and hepatitis B for those who are seronegative.(9, 33)

Pretreatment assessment of liver fibrosis or cirrhosis can be important as this may influence indication, strategy and success of treatment.(9, 11, 34) Abdominal ultrasound, liver biopsy or elastography are therefore part of the work-up. Liver biopsy remains the gold standard for

fibrosis assessment. Non-invasive tests such as transient elastography (FibroScan®) or the use of biomarkers may be useful to identify or exclude cirrhosis. However, the ability of Fibroscan® to discriminate between fibrosis stage F1 and F3 is limited.(35, 36)

Positive predictors of SVR with PR therapy can be classified as pretreatment or on-treatment factors. In general, the most important positive pretreatment predictors for SVR are: response to previous PR based treatment, e.g. naive patients and patients who relapsed to previous therapy respond better than partial and null responders (see Table 2 for classification of patients categories), interleukin (IL) 28B CC polymorphism (exclusively HCV genotype 1) and low stage of fibrosis. Other predictors are low baseline viral load (< 600.000 IU/ml), genotype non-1, non-HIV co-infection, age under 40 years, and non-black race.(37-39) The most important on-treatment positive predictive factor for achieving SVR is attaining a rapid viral response (RVR) (see Table 1).(40, 41) Other known on-treatment factors are decline in hemoglobin concentration during PR therapy in hepatitis C genotype 1, ribavirin plasma concentrations and treatment adherence.(42-44) With the use of DAAs, the predictive value of IL28B polymorphism is limited.(45) In addition, DAAs are more effective in genotype 1b than in genotype 1a patients.(3, 4, 46)

Table 2. Treatment categories according to the host response during previous treatment

Category	Characteristics
Naive patients	No previous treatment
Relapsers	HCV undetectable at end of treatment, but detectable after 24 weeks of follow-up
Partial responders	> 2 log HCV RNA decline at week 12, but detectable HCV RNA at week 24
Null responders	< 2 log HCV RNA decline at week 12
Non-responders	Null response or partial response
Viral breakthrough	Detectable HCV RNA at any time during treatment after previous undetectable HCV RNA during antiviral therapy

On-treatment laboratory testing should occur regularly, and should include HCV RNA (at the selected time points), hemoglobin, total leucocytes, neutrophils, thrombocytes and liver enzymes.

Indications and contraindications for antiviral therapy

Treatment should be considered in all patients who do not have contraindications, especially in those with METAVIR F3 and F4 and should be strongly considered in patients with METAVIR F2 fibrosis. In patients with METAVIR ≤F2 alternatively, therapy can be postponed until more DAAs have become available, allowing interferon free regimens.(9, 11, 34) There are subgroups with limited benefits from chronic hepatitis C treatment. First, elderly patients (age > 70 years) or patients with (longstanding) asymptomatic disease and low stage of fibrosis (METAVIR ≤ F2).(47) Second, absolute contraindications (such as decompensated cirrhosis or uncontrolled depression, psychosis, epilepsy, pregnancy or desire to have children, severe other medical diseases) and relative contraindications (such as thrombocytopenia < 90 x 10^9/l, neutrophil count < 1.5 x 10^9/l, anemia (hemoglobin < 8 mmol/l), renal insufficiency (GFR < 30 mL/min), or ongoing alcohol or drug abuse) may preclude therapy. In patients with relative contraindications benefits of treatment should be balanced carefully against the increased risk of side effects.(9, 48) Patients with concomitant HIV or HBV infection or other liver diseases and those with contraindications listed above, have been excluded from the phase 3 studies with boceprevir or telaprevir. As a consequence, treatment strategies formulated below cannot be applied to these patients. Finally, patients with virological failure on boceprevir or telaprevir therapy create a cohort of non-responders. Given the extensive cross resistance that can develop in patients failing either boceprevir or telaprevir retreatment with the other drug is not advisable.

If treatment is postponed, patients should be monitored yearly. Cirrhotic patients should be subjected to abdominal ultrasound for HCC screening once or twice a year.(49)

Antiviral therapy

Acute hepatitis C

Patients with acute HCV monoinfection should be treated if HCV RNA is still positive at 3 months after exposure, because spontaneous clearance is unlikely to happen at this stage.(26, 50) Therapy consists of peg-IFNα monotherapy (peg-IFNα-2a: 180 µg/week, peg-IFNα-2b: 1,5

µg/kg/week) for the duration of 24 weeks. With peg-IFNα monotherapy, SVR rates are more than 90%. The addition of ribavirin has no proven benefit.(26, 51)

Acute HCV infection is frequently reported in HIV co-infected male homosexual patients and for management the reader is referred to appropriate guidelines.(52, 53)

Chronic hepatitis C

Patients with HCV genotype 1

Both boceprevir and telaprevir can only be used in combination with PR for treatment of adult chronic HCV genotype 1 infected patients with compensated liver disease. Peg-IFNα and ribavirin dosage instructions are either peg-IFNα-2a 180 µg/week in combination with ribavirin 1000 mg (< 75 kg) or 1200 mg (≥ 75 kg) or peg-IFNα-2b 1,5 µg/kg in combination with ribavirin 800-1400 mg (< 65 kg: 800 mg, 65-80 kg: 1000 mg, 81-105 kg: 1200 mg, and > 105 kg: 1400 mg). Both peg-IFNα 2a or 2b, can be prescribed with either boceprevir or telaprevir.(54, 55)

Boceprevir and telaprevir both should be taken orally three times a day with eight hour intervals (boceprevir 800 mg three times daily, telaprevir 750 mg three times daily). Telaprevir should be taken with food (preferably containing at least 20 gram of fat) and boceprevir with a small meal to increase bioavailability.(56, 57)

There are no head-to-head studies that compare boceprevir and telaprevir, which makes it difficult to compare their relative efficacy.(58, 59) SVR rates are assumed to be comparable for both DAAs. The main differences are related to the side effect profiles, the use of a 4-week lead-in period with boceprevir, and the duration of DAA treatment.

With the new DAAs SVR rates have increased to 65-75% in treatment naive patients.(2-4, 60) Some 70-90% of patients who relapsed after PR treatment achieved SVR with boceprevir or telaprevir triple therapy compared to 25-30% in PR control arms. Partial responders obtained SVR in 40-60% with triple therapy compared to 7-15% with PR alone. Null responders achieved SVR in about 30% with telaprevir therapy in combination with PR, compared to 5% treated with PR alone (Figure 1 and 2).(5, 6)

significant proportion of naive patients (44-65%) in phase 3 studies with boceprevir or telaprevir in combination with PR met the criteria for response guided therapy (RGT) and can be treated for a shorter period (see 'Treatment strategies'). Success rates are very high in these patients (>90%).(2, 4) The main advantages of RGT are that it allows shortening of treatment and prevents unnecessary exposure to side effects.(61)

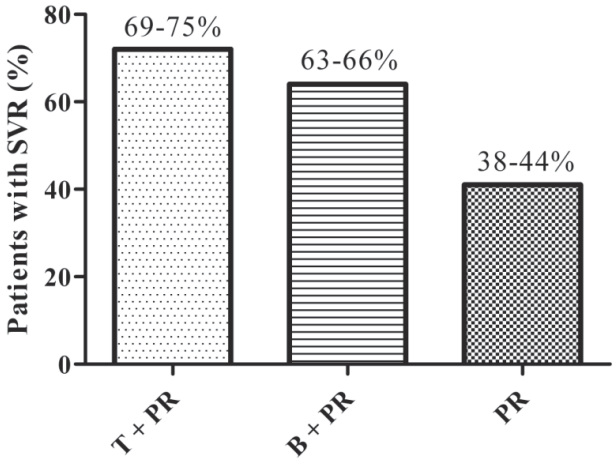


Figure 1. SVR rates in treatment naive patients with HCV genotype 1

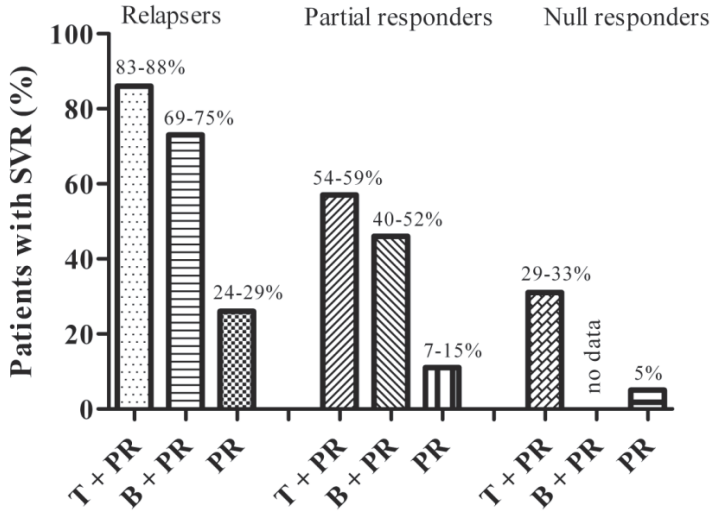


Figure 2. SVR rates in treatment experienced patients with HCV genotype 1

6

Treatment strategies

Depending on the host response during previous treatment and the presence of cirrhosis the optimal treatment strategy for both DAAs follows from figure 3 and 4. Important considerations about the implementation of these strategies are described here. First, regarding the stopping rules alternative time points and tolerated levels of viral load are used in DAA regimens. Second, the concept of RGT is dissimilar with respect to its duration and eligibility of patients. RGT can be applied for non-cirrhotic treatment naive patients

(boceprevir and telaprevir) and previous relapsers (telaprevir).(2, 4, 62) In these cases duration of treatment can be limited to 24 weeks (telaprevir) or 28 weeks (boceprevir) (Figure 3 and 4). Accurate quantitative and qualitative plasma HCV RNA measurement is crucial for choosing the right treatment strategy as this is the indicator for treatment success.(2-6) There are several test characteristics that need to be fulfilled: a lower limit of quantification of 25 IU/ml and a lower limit of detection of 10-15 IU/ml are mandatory in the DAA era. In this respect, RGT can only be applied when HCV RNA is undetectable at selected time points.(56, 57) It is important that a 'detectable but below the limit of quantification' HCV RNA result does not equal an 'undetectable' HCV RNA result.(63) A small proportion of naive chronic HCV genotype 1 patients with a RVR and favourable prognostic factors (low viral load < 600.000 IU/ml, ≤ F2 fibrosis, IL28B CC genotype) do not have added benefit from DAAs and can be treated with PR protecting them from DAA side effects.(64) In case RVR is not achieved, introduction of boceprevir at week 4 is recommended.(2) On the other hand, retreatment with DAAs in cirrhotic null responders should carefully be discussed considering the low SVR rates (~14%), the lack of alternatives, and likelihood of adverse events.(65)

Figure 3. Boceprevir treatment strategies

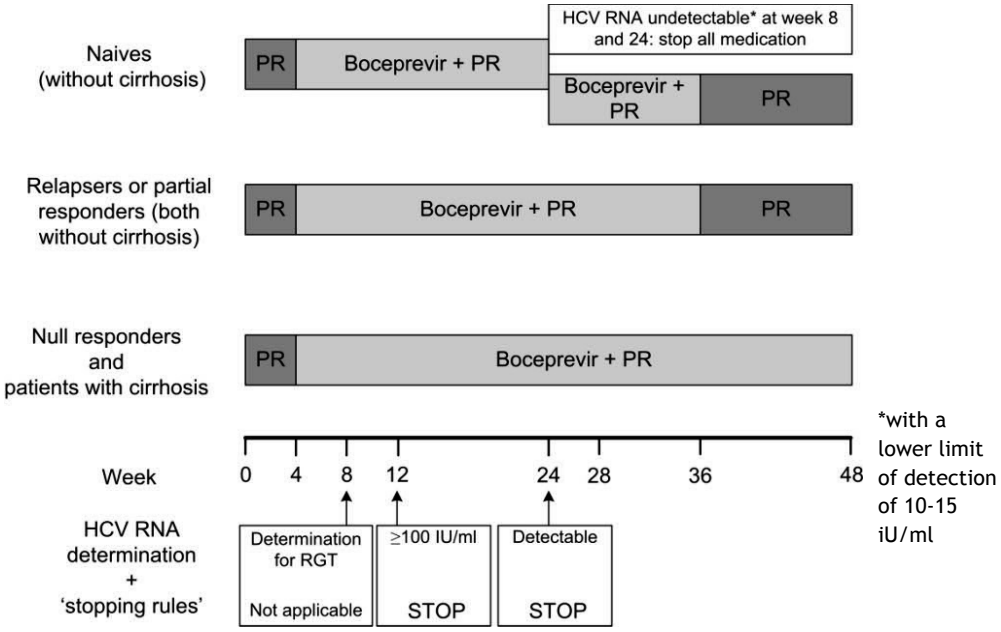
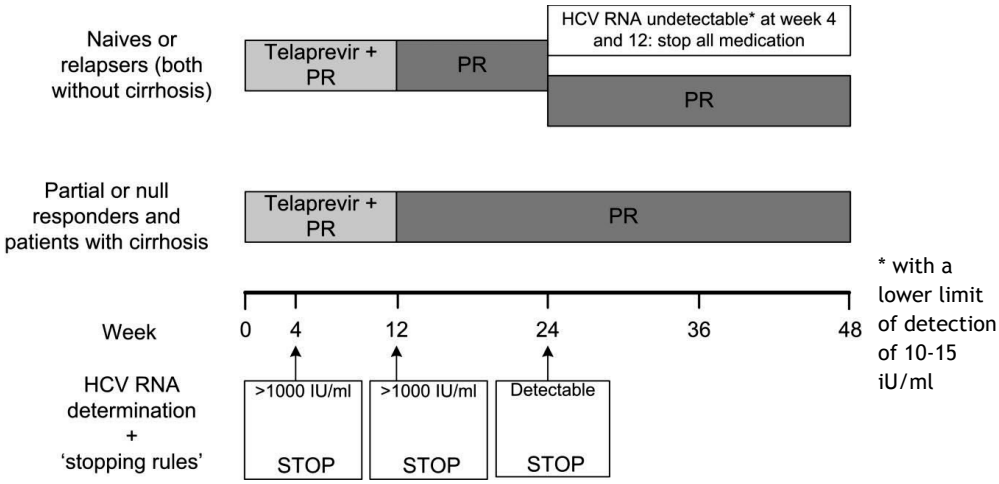


Figure 4. Telaprevir treatment strategies



Patients with HCV genotype 2 and 3

Boceprevir and telaprevir are not registered for treatment of chronic HCV genotype 2 and 3 infected patients.(66) Current treatment is 24 weeks of peg-IFNα-2a 180 µg/week or peg-IFNα-2b 1,5 µg/kg/week with ribavirin 800 mg. If there are baseline factors associated with a poor response ribavirin should be dosed weight based.(9) SVR rates are around 70-80% in these patients.(9, 67)

In case of intolerability for peg-IFNα dosage can be adjusted (peg-IFNα-2a 135 µg/week or peg-IFNα-2b 1,0 µg/kg/week) without compromising SVR rates. Sixteen weeks of treatment with peg-IFNα and weight based ribavirin can be applied to patients with a RVR, who cannot complete 24 weeks of treatment because of severe side effects. This strategy is only applicable for patients with favorable baseline factors (low viral load, fibrosis ≤ F2). However, with shortened therapy there is a slight increased risk of viral relapse in genotype 3 patients.(64, 68, 69).

In patients with chronic HCV genotype 2 and 3 infection without RVR and concomitant advanced liver fibrosis or cirrhosis or failure on previous treatment, a 48-week treatment strategy may be followed.(34, 67)

Patients with HCV genotype 4, 5 and 6

For genotype 4, 5 and 6 current PR consists of 48 weeks peg-IFNα with weight based ribavirin (see section 'antiviral therapy of HCV genotype 1 infection' for peg-IFNα and ribavirin dosage).

SVR rates range between 43-70%.(70) Naive genotype 4 patients with positive prognostic factors (≤ F2 fibrosis, low baseline viral load and a RVR) are eligible for shortened therapy of 24 weeks.(71, 72)

Viral resistance

Both boceprevir and telaprevir are highly specific inhibitors of the viral NS3/4A serine protease. The nucleoside sequence of the NS3/4A protease varies among HCV genotypes. As a result, the antiviral activity of the protease inhibitors differs between the HCV genotypes. Both DAAs were specifically designed for HCV genotype 1 and have limited activity against other genotypes.(66, 73, 74)

The high mutation rate results in a large diversity in the viral population, which may lead to the selection of protease inhibitor cross resistant variants, resulting in treatment failure. Therefore, both DAAs cannot be used as monotherapy and can only be prescribed in combination with PR to prevent the emergence of viral resistant strains.(75-77)

Drug-drug interactions

Boceprevir and telaprevir are substrates for CYP3A and P-glycoproteine (PgP).(56, 57) Compared to boceprevir, telaprevir is a stronger inhibitor of CYP3A and PgP. Drug interactions can be expected when both DAAs are used in combination with other drugs which are also CYP3A or PgP inhibitors or inductors enhancing the risk at drug toxicity or a decreased efficacy of the involved drugs. Because of the somewhat different profiles, interactions may vary between both agents. Therefore information and advice cannot be implemented equally for both boceprevir and telaprevir. Before treatment initiation with DAA-combination therapy we recommend to check for all possible interactions on http://www.hep-druginteractions.org/, the Dutch handbook for drug interactions with anti-HCV infection agents, and/or consult a pharmacist.(78, 79)

Some practical examples, the use of boceprevir and telaprevir leads to impaired efficacy of oral estrogen containing contraceptives, due to low estrogen concentrations. Therefore, the use of two nonhormonal containing contraceptives is recommended during and at least 2 months after cessation of boceprevir or telaprevir. (80, 81) Also, the use of both DAAs with simvastatin should be avoided as concomitant use results in increased drug levels of

simvastatin putting the patient at risk for rhabdomyolysis.(82, 83) Furthermore, drug levels of escitalopram, a frequent used selective serotonin reuptake inhibitor (SSRI), are lowered during boceprevir and telaprevir usage.(83)

Table 3 summarizes the most important interactions that should be avoided or interactions that require caution. If information on possible interactions is lacking, consider temporary discontinuation of the drug.

Table 3. Overview of drug-drug interactions with most frequently used co-medications in HCV-infected patients.[79]

Interacting agent*	**Anti-HCV agent ****	**CI**	**Management (M) Alternative (A)**
Alprazolam (ALP)	BOC, TVR		M: monitor for toxicity ALP A: oxazepam
Amlodipine (AML)	TVR		M: monitor for toxicity AML; start with 5 mg of AML A: BOC
Atorvastatin (ATO)	TVR	Yes	A: pravastatin
	BOC		M: monitor for toxicity ATO, max of 20 mg ATO/day A: pravastatin
Budesonide (BUD) inhalation, intranasally	BOC, TVR	Yes	A: beclomethasone
Carbamazepin (CAR)	BOC, TVR	Yes	A: valproic acid, lamotrigine, levetiracetam
Ciclosporin (CIC)	TVR		M: reduce CIC dose and/or extend dose interval; monitor CIC levels A: boceprevir and monitor CIC levels
Clarithromycin (CLA)	BOC, TVR		M: monitor for toxicity CLA and TVR A: azithromycine
Dexamethasone (DEX)	BOC, TVR		M: monitor for efficacy HCV PI
Diltiazem (DIL)	BOC, TVR		M: monitor for toxicity DIL A: low-dose amlodipine
Domperidone (DOM)	BOC, TVR	Yes	A: metoclopramide
Erythromycin (ERY)	BOC, TVR		M: monitor for toxicity ERY and TVR A: azithromycine
Escitalopram (ESC)	TVR		M: monitor for efficacy ESC, increase ESC dose if needed A: BOC
Ethinylestradiol (EE)	BOC, TVR	Yes	M: use two non-hormonal types of contraception

Felodipine (FEL)	BOC, TVR		M: monitor for toxicity FEL A; low-dose amlodipine
Fluticasone (FLU) inhalation, intranasally	BOC, TVR	Yes	A: beclamethasone
Itraconazole (ITR)	BOC, TVR		M: monitor for toxicity ITR and HCV PI; maximum of 200 mg ITR/day A: fluconazole
Ketoconazole (KET)	BOC, TVR		M: monitor for toxicity KET and HCV PI; maximum 200 mg KET/day A: fluconazole
Methadone (MET)	BOC, TVR		M: monitor for efficacy MET
	IFN		M: monitor for toxicity MET
Midazolam (MID), PO	BOC, TVR	Yes	A: temazepam or lorazepam or parenteral midazolam
Midazolam (MID), IV	BOC, TVR		M: reduce IV dose with 50%
Nicardipine (NIC)	BOC, TVR		M: monitor for toxicity NIC A: low-dose amlodipine
Nifedipine (NIF)	BOC, TVR		M: monitor for toxicity NIF A: low-dose amlodipine
Nisoldipine (NIS)	BOC, TVR		M: monitor for toxicity NIS A: low-dose amlodipine
Pimozide (PIM)	BOC, TVR	Yes	
Prednisone (PRE)	BOC, TVR	Yes	
Salmeterol (SAL)	BOC, TVR	Yes	A: formoterol
Sildenafil (SIL)	BOC, TVR		M: maximum of 25 mg SIL/48 h
Simvastatine (SIM)	BOC, TVR	Yes	A: pravastatin or BOC with low-dose atorvastatin
Sirolimus (SIR)	BOC, TVR	Yes	
St Janskruid (SJK)	BOC, TVR	Yes	
Tacrolimus (TAC)	TVR	Yes	
	BOC		M: reduce TAC dose and/or extend dose interval; monitor TAC levels A: ciclosporin
Tadalafil (TAD)	BOC, TVR		M: maximum of 10 mg TAD/72 h
Trazodone (TRA)	BOC, TVR		M: monitor for toxicity TRA, start with low-dose TRA
Triazolam (TRI)	BOC, TVR	Yes	A: temazepam of lorazepam
Vardenafil (VAR)	TVR		M: maximum of 2.5 mg VAR/72 h
	BOC		M: maximum of 2.5 mg VAR/24 h

Verapamil (VER)	BOC, TVR		M: monitor for toxicity VER A: low-dose amlodipine
Zolpidem (ZOL)	TVR		M: monitor for efficacy ZOL

* HIV medications are not listed

** BOC, boceprevir; TVR, telaprevir; RBV, ribavirin; IFN, interferon

Other abbreviations: CI, contraindicated;; IV, intravenous; HCV PI, hepatitis C virus protease inhibitor; INR, international normalized ratio

Side effects

PR treatment is frequently accompanied by side effects, such as flu-like symptoms, anemia, neutropenia, thrombocytopenia, and depression. These side effects influence quality of life and may result in dosage reduction or premature treatment discontinuation. This can be prevented by close monitoring and management of side effects.(42, 84)

With the addition of boceprevir and telaprevir to PR new side effects have emerged while other side effects may be aggravated.(85) For example, rash and (anal) pruritus affects ~50% of patients taking telaprevir while dysgeusia occurs in 40% of patients treated with boceprevir.(2-6) The most important side effects and their management strategies are discussed below

Anemia

Phase 3 trials have clearly shown that PR with boceprevir, but especially with telaprevir results in a higher frequency of anemia than PR alone.(2-6) Ribavirin dose reduction in patients treated with boceprevir or telaprevir does not compromise efficacy and is the first step of choice.(86, 87) Ribavirin should be reduced with 200 mg per step. During treatment ribavirin can be up titrated again when hemoglobin levels are acceptable (≥ 7.0 mmol/l). Dose reduction of ribavirin as opposed to dose maintenance supported by erythropoietin in patients with triple therapy is equally effective in terms of achieving SVR.(88) If used, erythropoietin agents should be discontinued when hemoglobin reaches the threshold of 7.5 mmol/l.(89) Blood transfusion should be saved for exceptional cases. For patients treated with PR (i.e. non genotype 1 patients) PR dose reduction should be postponed as long as possible as this negatively influences chance of SVR.(42) When interference is necessary, ribavirin or peg-IFNα dose reduction, use of erythropoietin agents or blood transfusions can be considered. No recommendation can be given for the preferred strategy.

Neutropenia

The incidence of neutropenia is higher in patients treated with PR in combination with a DAA. Although there is little evidence that neutropenia puts the patient at risk for an infection, current recommendations stipulate peg-IFNα reduction when neutrophil count falls below 0.75 x 10^9/l. Furthermore, (temporary) discontinuation of peg-IFNα should be performed when neutrophil count drops further (< 0.5 x 10^9/l).(9, 90) There is no room for granulocyte colony stimulating factor because of unclear benefit and high costs.(91)

Thrombocytopenia

Thrombocytopenia < 90 x 10^9/l is a relative contraindication for treatment of chronic HCV infection.(9, 92). Peg-IFNα reduction is recommended when platelet count drops below 50 x 10^9/l and should be discontinued when platelet count declines below 25 x 10^9/l. When platelet count increases again peg-IFNα can be restarted at a reduced dosage.(9)

Rash management

Rash is a common side effect of PR and occurs even more frequently with telaprevir. Moreover, 4-7% of patients in phase 3 trials assigned to telaprevir had to discontinue all antiviral therapy due to dermatological side effects. (3, 4, 6) It develops typically on the trunk, extremities and friction sites, it is mostly mild of nature and can be treated with local cooling ointment (unguentum emolliens) or with local corticosteroid therapy (class 3) and antihistamines. Patients with rash grade 2 to 4 need to be referred to a dermatologist without delay. (93) Severe rash (grade 3) is defined as involvement of more than 50% of body surface or if systemic symptoms occur (fever, lymphadenopathy, arthralgia, or rise in creatinine or ALT). In this case, telaprevir has to be discontinued and if there is no improvement within 1 week PR also needs to be discontinued.(94) Generally, rash will disappear within a couple of weeks after stopping telaprevir. Rare events with telaprevir are the Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), Stevens - Johnson syndrome (SJS) or Toxic Epidermal Necrolysis (TEN). All treatment should be stopped immediately, a dermatologist should be consulted immediately, and glucocorticoids should be considered.(94)

Psychiatric side effects

Psychiatric side effects such as depression, agitation, irritability, insomnia, lack of concentration and emotional instability puts the patient at risk for PR dose reduction, lower treatment adherence and premature treatment cessation resulting in lower SVR rates.(42, 95) Prophylactic treatment with a SSRI should be considered in all patients with a history of

depression or signs of depression at baseline. (96) Apart from pretreatment evaluation of feasibility of treatment and possible drug interactions, consider to consult a psychiatrist and/or a specialist in addiction medicine to ensure safety and drug compliance.

Follow-up after antiviral therapy

HCV RNA should be tested 24 weeks after the end of treatment. In case HCV RNA is negative, SVR is achieved and the patient can be considered to be cured from chronic HCV infection with only a minimal risk of viral recurrence.(97) Recent data suggest that negative HCV RNA 12 weeks post treatment is probably sufficient to confirm SVR, although this needs further evaluation.(98)

Hypothyroidism can arise during but also after termination of treatment. Consequently, thyroid function should also be assessed during the first 2 years after treatment.(84) Cirrhotic patients should be followed-up preferably in a specialized Dutch viral hepatitis center, because they still remain at risk for cirrhosis related complications. As per guidelines, abdominal ultrasound has been advised in the follow-up of these patients to screen for HCC and endoscopic assessment for esophageal varices.(49, 99)

The future

With the introduction of boceprevir and telaprevir the development of novel DAAs and immune modulatory therapy with less side effects than Peg-IFNα does not stop. There is intense interest for novel agents that avoid the use of peg-IFNα. Indeed, several HCV polymerase inhibitors are in advanced stages of clinical development. Without doubt therapeutic options will expand to other genotypes. In addition, efforts to design better options for difficult to treat patients (for example with HBV or HIV coinfections) will be necessary.

Furthermore, a new group of DAA non-responders will emerge. How and when these patients will be eligible for anti-HCV infection therapy is uncertain. Consequently, these patients will probably be excluded from upcoming trials with second generation DAAs, which means that at this time, treatment options for this group are limited.

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D

Discussion, summary in English and Dutch, addendum

7 General discussion

Part 1a

This thesis deals with clinical decision making in the therapeutic management of patients with a number of liver diseases. We have focused on infectious and non-infectious liver diseases where there is uncertainty or controversy with respect to medical treatment. We explored therapeutic options in autoimmune hepatitis, hepatitis delta, and hepatitis C infection. As a method we used the model of a systematic review for analyses of medical literature. We followed the Cochrane method in two of the four performed reviews. A Cochrane review is defined as a scientific endeavor with pre-planned methods section and assembly of original studies (predominantly randomized clinical trials, clinical controlled trials, and when there is no other evidence available observational studies) as their 'subjects'. The results of these multiple primary investigations are synthesized strategies limiting bias and random error. These strategies include a comprehensive search of all potentially relevant studies and the use of explicit, reproducible criteria in the selection of trials for review. A Cochrane review appraises primary research designs, study characteristics, data synthesis, and interpretation of results. This will yield information that facilitates medical decision making and will also identify knowledge gaps. Based on the experience of performing the Cochrane reviews, we provide the reader with recommendations on how to design new clinical trials in this field in the future.

Answers to questions addressed in this thesis:

Autoimmune hepatitis

What is the optimal induction and subsequent maintenance therapy for autoimmune hepatitis?

We performed a systematic review and examined all eleven randomized clinical trials for treatment of autoimmune hepatitis published from 1950 until July 2009 to answer this question. On the basis of these data we performed a descriptive analysis of the published randomized clinical trials.

The available randomized clinical trials show that both predniso(lo)ne monotherapy and predniso(lo)ne plus azathioprine combination therapy are able to induce a remission in autoimmune hepatitis. This strategy is equally effective in both treatment naive and relapsing patients and lead to lower mortality rate compared with azathioprine monotherapy.

We found that predniso(lo)ne plus azathioprine and azathioprine monotherapy are superior to predniso(lo)ne monotherapy in maintaining remission in autoimmune hepatitis. Mortality was absent in patients who were subjected to any of all three options.

These conclusions have some marginal notes. First, there was no standardized, universally accepted definition of remission before 1999. All included articles were published in or prior to 1999, and could consequently not match the overall definition and thus resulted in variations of used outcome measures between trials. Furthermore, the early randomized clinical trials in the 1970s included more severely affected patients. These trials contained more patients with cirrhosis, which led to worse treatment outcomes and a lower survival rate. Patients with less severe disease probably have not been included in the trials but are currently being treated in daily clinical practice. This hampers the generalizability of these trials.[1] There is a lack of data on mild autoimmune hepatitis, which could be due to publication bias.

Current literature indicates remission rates of 65–80% with conventional therapy.[2] We found much lower percentages of remission. Similarly, it has been shown recently that the application of the 2010 response criteria of the AASLD practice guidelines [3] compared with the 2002 criteria [4] lead to a lower remission rate (from 73% to 26%).[5, 6] Therefore, based on our review we conclude that either predniso(lo)ne monotherapy or predniso(lo)ne plus azathioprine combination therapy can be used in order to achieve remission. In patients that are in need for maintenance therapy, predniso(lo)ne plus azathioprine or azathioprine monotherapy are equally effective. However, these therapeutic options are far from ideal and the search for immunosuppressive agents with a favorable risk–benefit ratio continues.

Hepatitis delta

What is the available evidence for interferon-alpha in hepatitis delta therapy?

To address this question we performed a systematic review and examined all nine randomized clinical trials that used interferon-alpha-based treatment of hepatitis delta published from 1970 until January 2011.

Results from our analysis show that 1-year high dose interferon-alpha monotherapy is superior to 1-year pegylated interferon-alpha (peg interferon-alpha) in achieving undetectable levels or hepatitis delta virus ribonucleic acid (RNA - HDV RNA) and normal levels of alanine transaminase (ALT). The efficacy was not complete as only approximately 30% of hepatitis delta virus infected patients reached predefined endpoints.

Only, 48% of patients treated with high dose interferon-alpha monotherapy reached undetectable levels of HDV RNA after 1 year of treatment. This was considerably lower with peg interferon-alpha based treatment (22%). Similar results were achieved regarding reaching normal ALT levels. Fifty percent of patients on 1-year high-dose interferon-alpha therapy attained normal ALT levels. Again, this was superior to treatment with peg interferon-alpha therapy (31%).

In spite of our abovementioned results, we do not recommend to use high dose interferon-alpha in hepatitis delta infection. We advise to use peg interferon alpha therapy. The basis of this recommendation comes from the current use of peg interferon-alpha in hepatitis B and hepatitis C virus infection. In the last 15 years, peg interferon alpha has been developed especially for these two indications.[7-10] Science and drug development has progressed since the last trials with conventional interferon-alpha have finished. Unfortunately, no head-to-head trials have been performed and only indirect comparisons are possible for hepatitis delta infected patients. Furthermore, a major caveat in the earlier performed hepatitis delta trials has been identified. These earlier trials with interferon-alpha have used less sensitive HDV RNA assays and may have overestimated virological response rates compared with more recent trials with peg interferon-alpha treatment. All in all and also because of ease of use, it is reasonable to prefer peg interferon-alpha above conventional interferon-alpha.

Chronic hepatitis C

Is the administration or addition of aminoadamantanes in chronic hepatitis C treatment beneficial?

We performed two Cochrane systematic reviews with meta-analyses aimed at assessing benefits and harms of aminoadamantanes for chronic hepatitis C. We compared amantadine with placebo or no intervention. The second comparison was amantadine versus other antiviral drugs in the treatment of chronic hepatitis C infected patients. Both Cochrane systematic reviews did not demonstrate any significant effects of amantadine on all-cause mortality or liver-related morbidity in patients with chronic hepatitis C virus infection. We also assessed the effect on a secondary endpoint sustained virological response (SVR), but failed to demonstrate an advantage. However, subgroup analyses demonstrated that triple therapy with amantadine plus interferon-alpha and ribavirin compared with placebo or no intervention plus interferon-alpha and ribavirin increased the likelihood for SVR. On the contrary, we also compared amantadine with ribavirin with both the same additional therapy. Meta-analysis demonstrated that amantadine decreased the number of patients achieving SVR.

Since the introduction of amantadine, a wave of new therapies with direct-acting antiviral agents has emerged. These drugs hold the promise of higher efficacy, a better safety profile, and shorter treatment duration. Given this developing wave, it is better to wait for the results of trials that test these new therapeutic compounds, especially for patients who are not in immediate need for treatment. There are a number of direct-acting antivirals that target the specific sites of the hepatitis C protein such as the nonstructural (NS) NS3/4A protease, the NS5A protein, and the NS5B polymerase. Apart from the development of the two protease inhibitors (boceprevir and telaprevir) there are more than 40 new NS3/4A, NS5A, or NS5B inhibitors in the development pipeline.

Because of these new therapeutic modalities, we wrote a new Dutch guideline for hepatitis C virus infection. This guideline that brings recommendations for the management and treatment of hepatitis C infection became necessary with the introduction of boceprevir and telaprevir. These protease inhibitors entered the market in the Netherlands in 2012 as an adjunct to the standard of care for the treatment of chronic hepatitis C genotype 1 infected patients. Since the place of these drugs was unclear, it was needed to provide prescribing clinicians with a new updated guideline. The guideline is presented in Chapter 6.

Current literature shows that the safety profile for both boceprevir and telaprevir in a real-life setting is relatively poor.[11] This was especially evident in a subset of patients that had not been exposed to these drugs in the realm of randomized clinical trials that led up to the registration of these drugs. An observational real-life study, the so-called CUPIC cohort, in patients with advanced liver disease registered multiple complications and even mortality with these two new drugs.[11] Recommendations reproduced in our guideline are based on randomized clinical trials. Certain patient populations, for example patients with decompensated cirrhosis, were kept outside (whether intentionally) phase III randomized clinical trials. Randomized clinical trials preserve internal validity by strict inclusion and exclusion criteria, which may result in limited external validity. This leads to differences in treatment results and appearance of adverse events between patients included in clinical trials and the general practice.[11, 12]

After completion of our guideline the results from the phase III clinical trials with drugs such as ledipasvir, daclatasvir, and sofosbuvir have reached the journals.[13-15] These agents can achieve very high cure rates when combined with peg interferon-alpha and ribavirin, but have also started to provide promising results when combined in interferon-alpha-free, all-oral combinations. This development will make boceprevir and telaprevir superfluous given their poor safety profile as abovementioned.[11, 12]

What are the conclusions that we are able to draw? Based on our Cochrane systematic review we cannot support amantadine for clinical use in chronic hepatitis C infected patients. Boceprevir and telaprevir have improved treatment success in chronic hepatitis C, but also have safety issues. In case a patient is not in immediate need for treatment, i.e. patients with METAVIR ≤F2, therapy can be postponed until more direct-acting antiviral agents have become available with higher efficacy rates and a favorable safety profile.

Part 1b

Treatment has become possible for a wide spectrum of liver diseases. The evidence for these treatment options is highly variable. For some disorders the evidence is elaborate, for example chronic hepatitis C infection, while this is limited for other diseases such as hepatitis delta. This is not only due to the prevalence of the disorder, but is probably also related to the therapeutic targets. There is abundance of clinical trials in hepatology. However, the distribution is uneven and focused on those hepatological disorders where therapeutic targets are readily available. The purpose of the studies in this thesis was to reflect on the evidence obtained through these clinical trials using the (Cochrane) systematic review as research model. Therefore, we systematically reviewed and explored the evidence for some therapeutic targets for autoimmune hepatitis, hepatitis delta, and hepatitis C infection. This information allows us to provide the clinician with clear recommendations for therapy. Moreover, based on the explored information of the performed Cochrane systematic reviews, we obtained information to provide recommendations on how to design new clinical trials in this field in the future.

Systematic reviews

By performing systematic reviews we gained an overview of the quantity and the quality of the randomized controlled trials in the field of autoimmune hepatitis, hepatitis delta, and hepatitis C virus infection. There is a surprising variety in the number of randomized clinical trials describing the clinical efficacy of different treatment strategies among the studied hepatological disorders. The proportion of well executed clinical trials in autoimmune hepatitis patients is low. We found only 11 randomized clinical trials published between 1950 and July 2009. Furthermore, we detected a lack of randomized clinical trials describing the clinical efficacy of different treatment strategies in hepatitis delta treatment. Our search

yielded 13 randomized clinical trials published between 1970 and January 2011. Only two of them evaluated the efficacy of peg interferon-alpha. This is in sharp contrast to the situation in hepatitis C virus. There the number of randomized clinical trials describing the clinical efficacy of different treatment strategies in hepatitis C infected patients is very high compared to the situation in autoimmune hepatitis and hepatitis delta. We found more than 1600 randomized clinical trials published between 1950 and December 2013. Some, 44 randomized clinical trials described the clinical efficacy of aminoadamantanes. This uneven representation of clinical trials in different hepatological disorders is among others a result of the differences in prevalence and so in physical and economic burden of the disorders. There are more hepatitis C infected patients worldwide (around 170 million individuals worldwide) than there are patients with hepatitis delta and autoimmune hepatitis.[16-18] Vaccination against hepatitis B virus infection subsequently reduces the number of hepatitis delta infections because hepatitis delta only occur in individuals who are also infected with hepatitis B.[19, 20] Also, funding is an important element that determines which research topics are explored. Adequate funding, allows the design and execution of randomized clinical trials. Most funding goes to the development of promising drugs for highly prevalent or incident diseases. This leads to more randomized clinical trials performed in hepatitis C patients, than are in patients with hepatitis delta or autoimmune hepatitis. These hepatitis C trials generates more knowledge, more money, and this generates funding again to invest in new hepatitis C drug developments and trials. The development remains lagging in other areas.

Apart from differences in quantity of the clinical trials we also detected quality differences among trials for the described disorders. Most of the executed trials treating autoimmune hepatitis and hepatitis delta included only few patients. They were performed decades apart, with an evolving set of diagnostic criteria for autoimmune hepatitis. A definition for remission for autoimmune hepatitis is accepted since 1999. However, all trials were published in or prior to the determination of the definition of remission. Likewise, there is no standardized, universally accepted definition of remission in hepatitis delta. In both autoimmune hepatitis and hepatitis delta each included randomized clinical trial used their own end points. This makes it difficult to compare the included trials in a meta-analysis. Moreover, various doses of trial-treatment were used in the different trials, which also makes it difficult to compare the included trials with a meta-analysis. Follow-up duration was short in most trials. Longer follow-up will yield more information on treatment success, overall mortality, and liver related morbidity.

Evidence based medicine and Cochrane systematic review

To be a good physician, one should practice following evidence based medicine. Evidence based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research.[21] Best external evidence comes from systematic reviews of high-quality randomized clinical trials. These trials include homogeneous patient groups, with clear inclusion- and exclusion criteria, and uniform outcome measures. They are more likely to provide unbiased information than other study designs.

The Cochrane systematical review method is one of the methods to perform a systematic review. The Cochrane Collaboration recommends a domain-based evaluation tool for assessing risk of bias. With this tool critical assessments of internal validity ('quality assessment') are made separately for different domains. This relates to whether it answers its research question correctly. The used domains are: sequence generation, allocation concealment, blinding of participants and outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias. The extent to which potential sources of bias have been avoided influences the reliability of the results of a randomized trial.[22] In case the method of each domain is correctly described this indicates low risk of bias. When the method is not described or the method was not adequately performed, it suggests high risk of bias.

Another dimension is whether the trial is asking an appropriate question. This is part of 'external validity' and its assessment depends on the purpose for which the trial is used. External validity is closely connected with the generalizability or applicability of trials' findings.

Systematic reviews ask a specific clinical question, perform a comprehensive literature search, eliminate the poorly performed randomized clinical trials, and attempt to make practice recommendations based on the well-executed randomized clinical trials.[21] In case of no randomized clinical trials, this means no evidence based medicine. Treatment according to one randomized trial could mean no evidence based medicine. However, it is better to have one well-performed trial with a large population than more poorly-executed trials.

To achieve well-executed randomized clinical trials, quality criteria for performing these trials have been formulated in the recent years. Any new trial ought to be designed according to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines. These guidelines where developed in 2013 and followed the development of the CONSORT

statement. This statement, updated in 2010, is a minimum set of recommendations for reporting randomized clinical trials.[23-25] These CONSORT recommendations have contributed to the suboptimal improvement of the quality of randomized clinical trials.[26-28] These last few years witnessed an ongoing improvement of the quality of randomized clinical trials. The use of the CONSORT recommendations has resulted in some improvement of trials during the past 10 years. Without any doubt, the recent development of the SPIRIT guidelines, will similarly contribute to quality of performed trials

The Cochrane Collaboration also advises to design any further trial according to the SPIRIT guidelines and to conduct and report according to the CONSORT statement.[23-25] There are more than 8260 systematic reviews available that have been performed according to the Cochrane method. Twenty-four of the Cochrane reviews are discussing hepatitis C therapy. We select our two executed hepatitis C virus infection Cochrane reviews as format to describe the quality, the differences, and recommendations for improvement of uniformity.

Quality of included trials

What were the results in terms of quality of the included trials in our two Cochrane reviews about aminoadamantanes for chronic hepatitis C? In other words, did these researchers perform their trials correctly according to the different domains of the Cochrane method, in a way that is free from bias?

The generation of the allocation sequence was adequately described in 48% of the included trials in both systematic Cochrane reviews about aminadamantanes for chronic hepatitis C. One trial (= 2%) was judged as high risk of bias and the remaining 50% of trials were described as randomized but the method for random sequence generation was not described. The method used to conceal allocation was adequately described in 36% of trials. The method for allocation concealment was judged as unclear in 59% and as high risk of bias in two trials (5%).

The method of blinding of participants and personnel (performance bias) was adequately described in only 20%. Eighty percent of included trials were considered as high risk of bias concerning blinding of participants and personnel. Three trials (7%) adequately described the method of blinding of outcome assessment (detection bias). Thus, 93% of trials were judged as high risk of bias. Only two trials (5%) had low risk of bias according to both blinding of participants and personnel and blinding of outcome assessments.

Incomplete data (attrition bias) were addressed adequately in 39% of included trials. In 61% of trials there were risks of incomplete outcome data.

Pre-defined clinically relevant and reasonably expected primary and secondary outcomes were adequately assessed in only 14% of included trials. Accordingly, there were risks of selective reporting (reporting bias) of outcomes in 86% of included trials. Following the Cochrane Collaboration methods trials are judged low risk of bias relating to selective outcome reporting in case 1. The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; 2. The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified. This means, when a protocol is not present, the reviewers make a pre-specified list of expected outcome measures following the Cochrane Collaboration. In our both aminoadamantanes Cochrane reviews we included all our pre-defined primary and secondary outcome measures as expected outcome measures in case the study protocol was not available. This means we considered a trial as high risk of bias regarding reporting bias in case a protocol was not present and the trial did not report on all our included primary and secondary outcome measures (for example all-cause mortality, serious adverse events, SVR, etc.).

Six trials (14%) did not receive funding and were deemed to be of low risk of bias regarding vested interests. Forty-one percent of included trials received funding from the medical industry. It was unclear if trials received funding from medical industry in 45%. We considered these last 38 trials (86%) as having high risk of bias because industrial sponsorship could introduce bias.

Assessment of risk of bias is important as this may influence the reliability of the results. We found that none of the included trials had low risk of bias on all seven domains. Does this mean the results are not reliable? We do not think so. For example, what is the importance of blinding participants and outcome assessors with respect to SVR? Blinding is of importance for outcomes like quality of life. However, when measuring SVR, blinding of outcome assessors cannot influence the biomarker. The Cochrane systematic approach assesses clinical trials with a predefined analysis plan with list of expected outcomes. In case a protocol is not present and trials do not exactly report these pre-defined outcomes, these trials are judged as high risk of bias. The larger the list of predefined outcomes the more likely that there is a mismatch with outcomes reported in a particular clinical trial and the higher the chance that this trial will be marked with 'high risk of bias''.

As such use of stringent criteria bears the risk that we lose important information that is contained in these clinical trials. Many trials included in our reviews are rated as high risk of bias, partly because of poor reporting, partly because blinding was not applied. The introduction of the CONSORT statement should help to improve issues of poor reporting.[25]

Comparability of patients

Apart from assessing potential sources of bias, which could influence the reliability of the results, it is important to consider the population that has been allowed in the trials. The selection criteria should be sufficiently broad to encompass the likely diversity of trials, but sufficiently narrow to ensure that a meaningful answer can be obtained when trials are considered in aggregate.

The participants included in our both reviews met the pre-specified eligibility criteria: The diagnosis was based on presence of serum HCV RNA plus elevated transaminases for more than six months, or chronic hepatitis documented on liver biopsy. We also included patients diagnosed with 'non-A, non-B' chronic hepatitis as some trials may have been conducted before HCV RNA analyses were widely available. We excluded patients who had undergone a liver transplantation.

A total of 6384 patients with chronic hepatitis C were randomized to an amantadine arm or a control arm in the 44 clinical trials. Of the included patients more than 64% were males. All trials included adult patients, except for one trial which included children of one year old or more. Only one trial included human immunodeficiency virus co-infected patients. None of the trials included patients co-infected with hepatitis B virus infection.
Based on the existence of and response to previous antiviral treatment, the included patients were classified as naive (not previously treated with antivirals), relapsers (patients with a transient serological viral response to previous treatment with antivirals), or non-responders (patients without a serological viral response to previous treatment with antivirals). Most trials included naive or non-responder patients. However, heterogeneity can be introduced because of different definitions of non-responders were used in the different trials, like non-responder to previous interferon-alpha therapy alone or non-responder to combination therapy of interferon-alpha with ribavirin. Also, there could be heterogeneity among trials due to disease severity of patients at entry and differences according to genotype, which both can affect outcome measures.

Comparability of outcomes

The outcome measures in the included trials also preferably should be homogeneous. All included randomized trials in both Cochrane reviews about aminoadamantanes for chronic hepatitis C measured SVR as primary outcome measure. In general, the majority of randomized clinical trials in hepatitis C field assesses primarily SVR. However, SVR is a surrogate marker, why not determine outcomes which might be of more interest for patients and clinicians, such as all-cause mortality, liver-related morbidity, progression to hepatocellular carcinoma, and quality of life.[29] Recent large cohort studies showed a positive correlation between the presence of viremia and mortality.[30, 31] However, SVR is still only a putative (unvalidated) surrogate outcome for the patient-relevant intervention effect of antivirals according to current literature.[29, 32] Because randomized clinical trials need to inform clinical practice, clinical outcomes such as the risk of liver failure, hepatocellular carcinoma, mortality, and quality of life would be of greater interest to patients and clinicians. Most of these measures nevertheless require a follow-up of maybe up to five years. Currently, no randomized clinical trials assessing antiviral therapy are of such long duration. As a consequence, it is questionable whether for example all-cause mortality or risk of hepatocellular carcinoma, although highly relevant, are feasible as outcome measures in randomized clinical trials.

For quality of life it is possible to measure this in a shorter period than the abovementioned five years. Only six trials reported on quality of life out of the 44 included trials in both our aminoadamantanes Cochrane reviews. Three different questionnaires were used in these six trials. This indicates that there is no homogeneity considering measurement of quality of life. It is important that the field agrees on the instruments to assess quality of life, for example which questionnaire should be used.

Another interesting development is that recent data suggest that negative HCV RNA 12 weeks post-treatment is probably sufficient to confirm SVR.[33, 34] On the contrary, other data show that 12 weeks post-treatment using TaqMan polymerase chain reaction is less suitable for predicting persistent virological response.[35] This indicates there is conflicting and insufficient information, which suggests that further evaluation is necessary. Early determination of post-treatment response status in hepatitis C infected patients can help make decisions for the individual patients and might allow relapse patients to begin alternative therapy earlier. It is well established that low baseline viral load is associated with higher SVR rates.[36, 37] When negative HCV RNA 12 weeks post-treatment is sufficient to confirm SVR, this could mean that patients not achieving HCV RNA 12 weeks post-treatment

might benefit from early retreatment with different regimens or from inclusion in randomized clinical trials evaluating new antiviral drugs.

Advice regarding uniformity

By summarizing all the information about uniformity, we can make recommendations for new trials/research.

First regarding assessing risk of bias, which could influence the reliability of the results. After working with the domains for judging risk of bias, there are some considerations and recommendations.

Blinding is of importance for outcomes like quality of life. However, when measuring SVR, blinding of personnel cannot influence the laboratorial marker, blinding of personnel could be left out of the assessment of risk of bias. Concerning selective outcome reporting, it is important to mention the same outcome measures in the review as are presented in the protocol. For new trials we advise to report all data, also the negative outcomes. With the introduction of the SPIRIT and with the CONSORT statement this should be improved in new trials.[23-26]

Secondly, which type of patients should be included in the trials? An ideally executed trial include only adult patients or only children. Large number of patients are included in this ideal trial. Subgroups can be made, but also then the power of the subgroup should be large enough. With regard to gender, both can be included. However, again it is important to perform subgroup analysis and mention this in the paper of the trial. Furthermore, it includes only naive patients, only relapsers, or non-responders. Or it includes more than one of these groups, but then the results in the different subgroups are separately mentioned in the report of the trial. The same applies for differences in genotypes and differences in disease severity. Concerning genotype mention all the genotypes separately, not only genotype 1 infected patients or genotype non-1 infected patients, but genotype 1, genotype 2, genotype 3 infected patients, etc. Also considering disease severity it is of ideally divided into fibrosis grade 0, grade 1, grade 2, etc. Furthermore, again it is important to describe the subgroups, what were outcome measures in the subgroup with fibrosis grade 0 versus fibrosis grade 1, etc.

Third, regarding the outcome measures. It is important to make agreements for new trials about which outcome measures to assess. We think SVR should be the primary outcome measure. Also because a positive correlation between the presence of viremia and mortality

has been shown.[30, 31] However, mortality should be a second outcome measure, which yield a longer follow-up. Trials should include this longer follow-up period. Other clinical outcomes such as (serious) adverse events, the risk of liver failure, hepatocellular carcinoma, and quality of life are also important, which should be included in new trials. For quality of life it is important to make general agreements about which questionnaire should be used to measure quality of life and which time is needed to measure this.

Reflection

All in all, the Cochrane method is only one of the possible methods to perform a systematic review. Cochrane reviews focuses particularly on randomized clinical trials. The advantage of the Cochrane method is that they are well validated and robust. As such the Cochrane reviews are comparable and the quality of the evidence is immediately clear. On the other hand, the Cochrane method is really useful in those circumstances when the clinical trials that serve as input meet with the minimum (but already high) quality standards for risk of bias.

A different approach consists of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method.[38, 39] The GRADE system finds the quality of the available scientific research of importance when preparing a good guideline with recommendations. Usually a hierarchy of study design is used. Studies with low risk of bias and large size, such as meta-analyses and randomized trials, usually weight heavier than uncontrolled small studies, which could introduce higher risks of bias.[38] However, evidence is only one aspect necessary to draft recommendations. GRADE also takes into account the importance of the demonstrated effect for the patient. To make decisions on treatment some effects for patients are essential, other effects do not really matter.[40] To gather most essential evidence we think it is important to include a longer follow-up in new randomized trials. This will yield more information on treatment success, overall mortality, and liver related morbidity.

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Summary in English
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English Summary

We explored therapeutic options in autoimmune hepatitis, hepatitis delta, and hepatitis C infection. As a method we used the model of (Cochrane) systematic review for analysis of medical literature. This yield information that facilitates medical decision making but also identified knowledge gaps.

Chapter 1, 'the General Introduction', provides background information (epidemiology, pathogenesis, and therapeutic options) regarding autoimmune hepatitis, hepatitis delta, and hepatitis C infection. We also provide the model of systematic review that we applied to address our research questions.

In **Chapter 2** we describe the results of our systematic review of the optimal induction and subsequent maintenance therapy for autoimmune hepatitis. We examined all eleven randomized clinical trials for treatment of autoimmune hepatitis that were published from 1950 until July 2009. Seven trials evaluated induction therapy. These trials demonstrate that both predniso(lo)ne monotherapy and predniso(lo)ne plus azathioprine combination therapy are able to induce a remission in naive or relapsing patients with autoimmune hepatitis. Both treatment strategies lead to a lower mortality rate than treatment with azathioprine monotherapy. Four trials assessed maintenance therapy. They found that predniso(lo)ne plus azathioprine and azathioprine monotherapy maintained remission more often than predniso(lo)ne monotherapy in autoimmune hepatitis. Mortality was absent in patients who were subjected to any of three indicated options.

Chapter 3 presents the evidence for interferon-alpha in hepatitis delta infection that we systematically reviewed. We examined all nine randomized clinical trials that evaluated treatment with interferon-alpha for hepatitis delta. They were published before February 2011. Seven trials evaluated the treatment with interferon-alpha. The remaining two trials evaluated treatment with pegylated interferon-alpha (peg interferon-alpha). Results from our analysis show that 1-year high-dose interferon-alpha monotherapy is more effective than 1-year peg interferon-alpha in achieving undetectable levels of hepatitis delta virus ribonucleic acid (HDV RNA) and normal levels of alanine aminotransferase (ALT).

Next, we delineate treatment with aminoadamantanes versus placebo or no intervention for chronic hepatitis C infection in **Chapter 4** according to the Cochrane systematical review method**. Chapter 5** also follows the Cochrane systematic method and focuses on treatment with aminoadamantanes for chronic hepatitis C infection, but in this case compared with other antiviral drugs. Both Cochrane systematic reviews did not demonstrate any significant effects

of amantadine on all-cause mortality or liver-related morbidity or on achieving a sustained virological response (SVR) in patients with chronic hepatitis C virus infection. However, subgroup analyses demonstrate that triple therapy with amantadine plus interferon-alpha and ribavirin compared with placebo or no intervention plus interferon-alpha and ribavirin increased the likelihood for obtaining a sustained virological response. We also compared amantadine with ribavirin with both the same additional therapy. Meta-analysis demonstrates that amantadine decreased the number of patients achieving SVR.

Since the introduction of amantadine, a wave of new therapies with direct-acting antiviral agents has emerged. Because of these new therapeutic modalities, we wrote a new Dutch guideline for hepatitis C virus infection. **Chapter 6** describes the current treatment guideline of chronic hepatitis C infection. This guideline that brings recommendations for the management and treatment of hepatitis C infection became necessary with the introduction of boceprevir and telaprevir, which entered the market in the Netherlands in 2012 as an add-on to the standard of care (peg interferon-alpha and ribavirin).

We complete this thesis by a General Discussion (**Chapter 7**) that summarizes and discusses the main findings of this thesis. Furthermore, based on the experience of performing the (Cochrane) reviews, we provide the reader with recommendations on how to design new clinical trials in this field in the future.

Nederlandse samenvatting

In dit proefschrift hebben we de therapeutische opties voor auto-immuun hepatitis, hepatitis delta en chronische hepatitis C infectie onderzocht. Voor een grondige analyse van de medische literatuur hebben we het model van een systematische review gebruikt. Dit levert nuttige informatie voor de medische besluitvorming en het vergemakkelijkt tevens het identificeren van leemtes in onze kennis.

Hoofdstuk 1, 'de algemene inleiding', geeft achtergrondinformatie (epidemiologie, pathogenese en therapeutische opties) met betrekking tot auto-immuun hepatitis, hepatitis delta en chronische hepatitis C infectie. Wij tonen ook het model dat we hebben toegepast om onze onderzoeksvragen te beantwoorden. Dit model, de (Cochrane) systematische review, volgt een nauwgezet pad om de literatuur te analyseren en is de huidige standaard op dit gebied.

In **Hoofdstuk 2** beschrijven we de resultaten van onze systematische review over de optimale inductie en verdere onderhoudsbehandeling voor auto-immuun hepatitis. Wij hebben alle elf gerandomiseerde klinische studies onderzocht die behandeling van auto-immuun hepatitis hebben bestudeerd en gepubliceerd vanaf 1950 tot juli 2009. Zeven studies hebben een inductie therapie geëvalueerd. Deze studies tonen aan dat zowel prednison monotherapie als prednison plus azathioprine combinatietherapie in staat is om een remissie te induceren bij patiënten met auto-immuun hepatitis die niet eerder zijn behandeld of die een relapse hebben doorgemaakt. Beide behandelingsstrategieën leiden tot een lager sterftecijfer dan de behandeling met azathioprine monotherapie. Vier studies hebben onderhoudstherapie onderzocht. Deze tonen aan dat prednison plus azathioprine en azathioprine monotherapie vaker remissie induceren dan prednison monotherapie. Mortaliteit was afwezig bij patiënten die werden behandeld volgens een van de drie opties.

Hoofdstuk 3 toont het bewijs voor behandeling met interferon-alfa bij patiënten geïnfecteerd met hepatitis delta. We hebben de analyse verricht met een systematische review. Alle negen gerandomiseerde klinische studies die behandeling met interferon-alfa voor hepatitis delta hebben geëvalueerd, hebben wij onderzocht. Alle negen studies zijn vóór februari 2011 gepubliceerd. Zeven studies onderzochten behandeling met interferon-alfa. De overige twee studies evalueerden behandeling met gepegyleerd interferon-alfa (peg interferon-alfa). Resultaten van de analyse tonen aan dat 1-jaar behandeling met alleen hoge dosis interferon-alfa effectiever is dan 1 jaar peg interferon-alfa in het bereiken van ondetecteerbare waarden van hepatitis delta RNA virus en normale waarden van alanine aminotransferase (ALAT).

We beschrijven de behandeling met aminoadamantanes vergeleken met placebo of geen interventie voor chronische hepatitis C infectie in **Hoofdstuk 4**. Dit onderzoek is uitgevoerd door middel van een systematische review volgens de Cochrane methode. **Hoofdstuk 5** volgt ook de Cochrane methode voor systematische review en richt zich eveneens op behandeling met aminoadamantanes voor chronische hepatitis C infectie, maar dan vergeleken met andere antivirale middelen. Beide systematische reviews tonen aan dat amantadine, een aminoadamantane, geen positieve invloed heeft op sterfte, op lever gerelateerde morbiditeit en op het bereiken van een 'sustained virologic response' (SVR). Dit is klaring van hepatitis C RNA virus uit het bloed zes maanden na het stoppen van de behandeling, bij patiënten met een aangetoonde chronische hepatitis C infectie. Echter, subgroep analyse toont aan dat behandeling met amantadine, interferon-alfa en ribavirine in vergelijking met placebo of geen interventie gecombineerd met interferon-alfa en ribavirine een verhoogde kans geeft op het behalen van een 'sustained virologic response'. Ook hebben we behandeling met ribavirine vergeleken met behandeling met amantadine, beiden met dezelfde aanvullende therapie (bijvoorbeeld interferon-alfa). Meta-analyse toont aan dat het aantal patiënten dat een SVR behaalt met behandeling met amantadine lager is dan met behandeling met ribavirine.

Sinds de introductie van amantadine zijn er nieuwe therapieën in ontwikkeling gekomen. Gelet op deze nieuwe therapeutische mogelijkheden, hebben wij een nieuwe Nederlandse richtlijn geschreven voor hepatitis C infectie. **Hoofdstuk 6** beschrijft de huidige behandelingsrichtlijn van chronische hepatitis C infectie. Deze richtlijn geeft aanbevelingen voor management en behandeling van hepatitis C infectie, in het licht van de introductie van boceprevir en telaprevir. Deze twee proteaseremmers zijn in Nederland in 2012 op de markt gekomen als een aanvulling op de standaard behandeling (peg-interferon-alfa en ribavirine).

Dit proefschrift wordt afgesloten door een algemene discussie in **Hoofdstuk 7** waarin de belangrijkste resultaten worden samengevat en bediscussieerd. Bovendien bieden wij de lezer aanbevelingen, gebaseerd op de ervaring opgedaan bij het uitvoeren van de (Cochrane) reviews, hoe nieuwe klinische onderzoeken op dit gebied in de toekomst te ontwerpen en uit te voeren.

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Curriculum Vitae

Mieke Lamers (17 december 1983) groeide op in Niftrik (Gelderland). Ze volgde het Voorbereidend Wetenschappelijk Onderwijs aan het Maaswaal College te Wijchen. In september 2002 startte ze met de opleiding Geneeskunde aan de Radboud Universiteit te Nijmegen. Na het behalen van haar artsexamen in december 2008 startte Mieke als sub-investigator van klinisch onderzoek in diverse deelgebieden op de afdeling Maag-, Darm- en Leverziekten van het Radboudumc (destijds nog UMC St Radboud). Ook verrichtte zij klinische werkzaamheden op de hepatitis polikliniek. In de tussentijd begon Mieke met review onderzoek op het gebied van verschillende typen hepatitis onder leiding van prof. dr. J.P.H. Drenth en ging zij drie maanden naar de Kopenhagen Clinical Trial Unit voor het schrijven van een Cochrane review onder leiding van dr. C. Gluud. Sinds 1 maart 2013 is Mieke gestart met de opleiding tot specialist ouderengeneeskunde aan de VOSON Nijmegen (opleider: drs. E. van der Geer).

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